PB86-117967

Drinking Water Criteria Document for Endrin

Environmental Criteria and Assessment Office
Cincinnati, OH

Mar 85

U.S. Department of Commerce
National Technical Information Service
NTIS

FINAL DRAFT
ECAO-CIN-423
March, 1985
EPA-600/X-84-176-

United States
Environmental Protection
Agency

EPA

PB86-117967

Research and Development

DRINKING WATER CRITERIA DOCUMENT FOR ENDRIN

Prepared for

OFFICE OF DRINKING WATER

Prepared by

Environmental Criteria and
Assessment Office
Cincinnati OH 45268

DRAFT: DO NOT CITE OR QUOTE

NOTICE

This document is a preliminary draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comments on its technical accuracy and policy implications.

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

2.

3. RECIPIENT'S ACCESSION NO.
PB86 117967 /AS

SUBTITLE
Drinking Water Criteria Document for
Endrin

5. REPORT DATE
3/85

6. PERFORMING ORGANIZATION CODE

HOR(S)
Environmental Protection Agency

8. PERFORMING ORGANIZATION REPORT NO.

PERFORMING ORGANIZATION NAME AND ADDRESS

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.

12. SPONSORING AGENCY NAME AND ADDRESS
U.S. Environmental Protection Agency
Office of Drinking Water (WH-550)
401 M St., S.W., Washington, D.C. 20460

13. TYPE OF REPORT AND PERIOD COVERED
Scientific review

14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on endrin. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of endrin
- Toxicokinetics and human exposure to endrin
- Health Effects of endrin in humans and animals
- Mechanisms of toxicity of endrin
- Quantification of toxicological effects of endrin

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Endrin properties Endrin exposure Endrin toxicity Drinking Water		

18. DISTRIBUTION STATEMENT
OPEN

19. SECURITY CLASS *(This Report)*
Non-sensitive

20. SECURITY CLASS *(This page)*
Non-sensitive

21. NO. OF PAGES
195

22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DOCUMENT DEVELOPMENT

Cynthia Sonich Mullin, M.S., Document Manager
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Helen H. Ball, Project Officer
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Authors

Shane S. Que Hee, Ph.D.
University of Cincinnati

Martha Radike, Ph.D.
University of Cincinnati

Evelyn Widner, B.S.
University of Cincinnnati

Rita Schoeny, Ph.D.
University of Cincinnati

Ellen O'Flaherty, Ph.D.
University of Cincinnati

Stuart Baxter, Ph.D.
University of Cincinnati

Scientific Reviewers

Randall J.F. Bruins, M.S.
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Margaret L. Chu, Ph.D.
Carcinogen Assessment Group
U.S. Environmental Protection Agency
Washington, DC

Peter Gartside, Ph.D.
University of Cincinnati

Richard Hertzberg, Ph.D.
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Keith Jacobson, Ph.D.
Life Systems, Inc.
Arlington, VA

Geraldine Kraegar, Ph.D.
University of Cincinnati

Robert McGaughy, Ph.D.
Carcinogen Assessment Group
U.S. Environmental Protection Agency
Washington, DC

Jennifer Orme, M.S.
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

Yogendra Patel, Ph.D.
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC

William Bruce Peirano, M.S.
Environmental Criteria and Assessment Office, Cincinnati
U.S. Environmental Protection Agency

William E. Pepelko, Ph.D.
Carcinogen Assessment Group, OHEA
U.S. Environmental Protection Agency
Washington, DC

Editorial Reviewers

Erma Durden, B.S.
Environmental Criteria and Assessment
  Office, Cincinnati
U.S. Environmental Protection Agency

Judith Olsen, B.S.
Environmental Criteria and Assessment
  Office, Cincinnati
U.S. Environmental Protection Agency

Document Preparation

Technical Support Services Staff: C. Cooper, P. Daunt, C. Fessler, K. Mann, B. Zwayer, Environmental Criteria and Assessment Office, Cincinnati

Other Contributers: Becky Clark, Peter Gartside, Kay Irion, Geraldine Kruecer, Lorraine Mercer, Ted Morris, Jane Onslow, Maria Zinam, University of Cincinnati

TABLE OF CONTENTS

Page

I. SUMMARY I-1

II. PHYSICAL AND CHEMICAL PROPERTIES. II-1

  SPECTROSCOPIC PROPERTIES II-11
  CHEMISTRY. II-11
  ANALYTICAL METHODS II-12
  SUMMARY. II-14

III. TOXICOKINETICS. III-1

  ABSORPTION III-1
  ORAL III-1
  INHALATION III-3
  DERMAL III-3
  DISTRIBUTION AND METABOLISM. III-4

    Distribution in Human Tissues III-4
    Distribution in Animal Tissues. III-7

  MECHANISMS OF TRANSPORT AND METABOLISM III-23
  ELIMINATION. III-26
  SUMMARY. III-33

IV. HUMAN EXPOSURE. IV-1

  EXPOSURE ESTIMATION. IV-2

    Drinking Water. IV-2
    Diet. IV-4
    Air IV-6

  SUMMARY. IV-6
  REFERENCES IV-10

V. HEALTH EFFECTS ON ANIMALS V-1

  ACUTE TOXICITY V-1

    Experimental Lethality Studies. V-1
    Environmental and Accidental Intoxication V-10
    Cardiovascular Effects. V-13
    Tissue Concentration as Indicator of Lethal Dose V-14
    Enzyme Activity V-19

Page

OTHER EFFECTS. V-22
SUBACUTE EFFECTS OF ENDRIN V-22
CHRONIC EFFECTS. V-25
INTERACTIONS V-32
TERATOGENICITY AND REPRODUCTIVE EFFECTS. V-35

Mammals V-35

MUTAGENICITY V-42
CARCINOGENICITY. V-44
SUMMARY. V-59

VI. HEALTH EFFECTS ON HUMANS. VI-1

ACUTE TOXICITY VI-1

Accidental and Intentional Poisonings VI-1
Effects of Occupational Exposures VI-3
Immunology. VI-3
Epidemiological Studies VI-3

SUMMARY. VI-8

VII. MECHANISMS OF TOXICITY. VII-1

ACUTE TOXICITY VII-1

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS VIII-1

EXISTING GUIDELINES, RECOMMENDATIONS AND STANDARDS . . . VIII-4
NONCARCINOGENIC EFFECTS. VIII-6
QUANTIFICATION OF TOXICOLOGICAL EFFECTS. VIII-10

Derivation of 1-Day HAs VIII-10
Derivation of 10-Day HAs. VIII-12

DERIVATION OF LIFETIME AADI. VIII-14
CARCINOGENIC EFFECTS VIII-15
SPECIAL CONSIDERATIONS VIII-18
SUMMARY. VIII-20

IX. REFERENCES. IX-1

LIST OF TABLES

No.	Title	Page
II-1	Nomenclature, Indexing Terms and Synonyms Currently Used for Endrin	II-3
II-2	Chemical Information Related to Some Endrin Degradation Products	II-4
II-3	CAS Indexing Terms and CAS RN for Endrin Metabolites	II-5
II-4	Typical Composition of Technical Grade Endrin	II-6
II-5	Some Pesticide Mixtures in which Endrin is not the Only Pesticide	II-8
II-6	Analytical Methods for Determining Endrin or Endrin Transformation Products in Tissues or Animal Fluids	II-13
III-1	Evidence of Absorption Using Residue and Biological Effect Data	III-2
III-2	Endrin Concentrations Found in Victims of Endrin Poisoning	III-6
III-3	Distribution of Endrin and 12-Ketoendrin at Day 148 in Sykes Hybrid III Hens (2 kg initially) Fed 0.13 mg/kg Diet by Capsule	III-10
III-4	Radioactivity in Tissues of Five Hens After a 148-Day Period of Treatment with 0.3 μCi/Day	III-11
III-5	Endrin Distribution in Birds in the Post-1978 Literature	III-13
III-6	Distribution of Endrin and 12-Ketoendrin in Experimental Animals	III-17
III-7	Distribution of Radioactivity in Various Experimental Animals after an Acute Oral Dose of Endrin	III-19
III-8	Analysis of Urine from Endrin Plant Workers in England	III-30
III-9	Estimated Half-Lives in Various Sources for Elimination of Endrin Administered by the Oral Route	III-32
IV-1	Estimated Daily Intake of Endrin from Drinking Water	IV-3
IV-2	Estimated Total Daily Dietary Intake of Endrin for Adult Male, Infant and Toddler	IV-5

No.	Title	Page
IV-3	Estimated Daily Respiratory Intake of Endrin.	IV-7
IV-4	Estimated Daily Intake of Endrin from the Environment by Adult Males.	IV-9
V-1	Acute Toxicity of Endrin in Experimental Animals.	V-2
V-2	Median Lethal Doses 10 Days After Oral Administration of Endrin and Its Metabolites to Rats	V-6
V-3	Endrin Short-Term Dietary LC_{50} Values	V-8
V-4	Tissue Concentrations in Brain as Indicators of Lethal Doses of Endrin in Selected Species of Warm-Blooded Animals	V-16
V-5	Mortality of Animals Exposed to 0.36 ppm (5.62 mg/m^3) Endrin Vapor.	V-26
V-6	Weight Loss and Liquid Content (Mean % ± S.E.) of Quail Carcasses After Technical Chlordane, 98%-Pure Endrin, and Chlordane-Endrin Treatments	V-34
V-7	Teratogenicity and Reproductive Studies Performed with Endrin in the 1960's.	V-36
V-8	Reproductive Effects of Endrin for Studies Performed Since 1970.	V-38
V-9	Negative Studies of the Carcinogenic Potential of Endrin. .	V-45
V-10	Incidence of Malignant Tumors in Male Rats Ingesting Endin	V-48
V-11	Incidence of Malignant Tumors in Female Rats Ingesting Endin	V-49
V-12	Number of Osborne-Mendel Female Rats with Carcinomas. . . .	V-52
V-13	Number of Osborne-Mendel Male Rats with Carcinomas.	V-53
V-14	Number of Osborne-Mendel Female Rats with Benign Tumors.	V-55
V-15	Number of Osborne-Mendel Male Rats Ingesting Endrin with Benign Tumors.	V-56
VI-1	Description of Plants Included in the Study of Manufacturers of Organochlorine (OC) Pesticides	VI-7
VIII-1	Summary of Data Used to Derive HA or AADI	VIII-16

LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
ATP	Adenosine triphosphate
bw	Body weight
CNS	Central nervous system
DNA	Deoxyribonucleic acid
dw	Dry weight
EC	Extraction chromatography
EEG	Electroencephalogram
GC	Gas chromatography
HA	Health advisory
i.p.	Intraperitoneal
i.v.	Intravenous
LD_{50}	Lethal dose to 50% of the recipients
LD_{90}	Lethal dose for killing 90% of the recipients
MEL	Minimal effect level
MS	Mass spectroscopy
NADPH	Nicotinamide adenine dinucleotide phosphate dehydrogenase
NAPH	Nicotinamide adenine dinucleotide dehydrogenase
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
ST_{50}	Survival time of 50% of the recipients
TLC	Thin-layer chromatography
TLV	Threshold limit value
TWA	Time-weighted average
ww	Wet weight

I. SUMMARY

Endrin is an aliphatic organochlorine cyclodiene pesticide first introduced into the United States in 1951. It is produced by the epoxidation of isodrin obtained from the reaction of hexachlorocycloheptadiene and cyclopentadiene. It has been produced in the United States by the Velsicol Chemical Corporation. Endrin currently has limited uses (1979 usage: 176 megagram) in the cotton growing regions of western Oklahoma, western Texas, New Mexico, Arizona and California. It controls pale-western and army-cutworms and grasshoppers, as well as eastern pine voles, western meadow voles, sugar cane beetle and treats conifer seeds.

Endrin is a compound of low solubility in water, high solubility in non-polar organic solvents, low vapor pressure (2.7×10^{-7} mm Hg at 25°C), high adsorptive potential in high organic-content soils, and a large octanol/water coefficient (2.18×10^{5}).

The major analytical methods for endrin include extraction, column chromatography and gas chromatography/mass spectrometry (GC/MS). Acidification or high temperatures will decompose endrin. Endrin has low recoveries from waters at pH 2 (23%), but >80% recoveries at pHs >7. In contrast, its acid decomposition product, endrin ketone, is well recovered from waters at all pHs. The photodecomposition product, the half-cage ketone, has also been found in environmental media. Spills of endrin in the environment have been detoxified by reaction with acidified zinc dust. Standard U.S. EPA and NIOSH analytical methods are used for measuring endrin.

Endrin has occasionally been found in drinking water and in food; tissue analysis of the general population have ever been found to contain endrin residues. Endrin is absorbed through the skin, by the lungs and by the gut, but no quantitative rates are known. Animals, birds and humans who have been exposed to large amounts of endrin have shown residues. In all species, endrin is quickly metabolized and its metabolites quickly eliminated. Endrin deposition in tissues, especially fat, does occur at high doses in experimental animals and in birds. Residues have been detected in liver, brain, kidneys and fat. Endrin has a weighted average bioconcentration factor (BCF) of 3970 for the edible portion of all freshwater and estuarine fish and shellfish consumed by United States residents. Poisoning incidents have occurred in animals and man, convulsions in man are known to occur above doses of 0.2 mg endrin/kg bw. Blood residues have been found in humans grossly exposed to endrin in occupational and poisoning incidents. Endrin poisoning incidents have been documented in Wales, the United Arab Republic, Qatar and Saudi Arabia. The major toxicant in mammals is considered to be the metabolite, 12-ketoendrin, but endrin itself is considered the toxicant in birds; residues in brains are also supportive of these hypotheses. Modes of elimination are species dependent, but in mammals the measured and calculated half-lives of endrin derived material are between 1 and 4 days. The major metabolite in mammals is anti-12-hydroxyendrin glucuronide and the D-glucaric acid level in the urine is an indicator of exposure dose. Hydroxylation at the 3-position, epoxide hydration and production of 12-ketoendrin also occur. Endrin penetrates the placental barrier in rats, mice and hamsters. In rats, >50% of endrin-derived material is eliminated within 1 day in the bile as glucuronides, which after enterobacterial degradation and enterohepatic circulation are eliminated as aglycones in the feces. Excretion occurs slower in females than in males. Cows excrete free anti-12-hydroxyendrin conjugated in the urine as the sulfate. This also occurs in hens. The anti-12-hydroxyendrin has been detected as the glucuronide in the urine and feces of humans. Hens appear to eliminate endrin faster than other birds; with endrin itself being excreted. Endrin accumulates more in birds than in mammals.

Exposure to endrin in humans causes central nervous system effects, convulsions (above 0.2 mg/kg body weight), and in some cases, death (>6 g/person). In endrin intoxication cases, electroencephalograms show paroxysms of predominantly bilateral synchronous theta waves. In mild poisoning, recovery is usually rapid and there are no permanent effects. This is consistent with short half-lives of elimination. Epidemiology studies have corroborated the existence of convulsions and other central nervous systems effects in endrin-exposed workers.

Exposure to animals reveals that the acute oral LD_{50} to mammals ranges from 2.3 to 43.4 mg endrin/kg bw. After dermal exposure LD_{50} values range from 11-92 mg endrin/kg bw and are vehicle-dependent. Inhalation exposure to 5.62 μg endrin/m³ for 7 hours over 130 days is not lethal to rats, hamsters and guinea pigs. Young animals are more sensitive than adult animals to the effects of endrin.

In the early chronic studies of Treon, et al. (1955), 1 mg endrin/kg feed produced no effects with respect to changes in body weight and mortality in rats and dogs; however, Reuber (1978) concluded that 0.1 mg/kg diet induced excess malignancies in rats. NCI studies (1979) did not indicate that endrin was a carcinogen but Reuber (1978) disputed this. Unfortunately, the NCI studies were defective in not including an appropriate control group, and reassessments of histological slides from the NCI studies (Reuber, 1979) are controversial. Since endrin is not a direct-acting mutagen, and since it appears to have some properties of a promoter, endrin is probably not carcinogenic. However, clear demonstration of carcinogenicity is complicated by the toxicity of the chemical, and it is possible that the nondose response observed by Reuber (1978) is caused by toxicity considerations.

Endrin caused morphologic teratogenicity in mice and hamsters but not in rats and was a behavioral teratogen in all these species. The NOEL in rats in relation to maternal weight gain and behavioral activity was ~0.075 mg endrin/kg bw/day administered from day 7 to day 15 of gestation. Fetal toxicity in Syrian Golden hamsters occurred at doses >0.75 mg endrin/kg bw/day from day 5-14 of gestation and appeared correlated with either the appearance of 12-ketoendrin in the fetus or the presence of a critical level of endrin in the fetus.

Endrin appears to be more toxic to female birds than to male or female mammals, the acute oral LD_{50} to pigeons being 1.2-2.0 mg/kg bw and that to female mallards being 5.6 mg endrin/kg bw. Residues of >0.6 mg endrin/kg ww of brain in birds (bald eagles, grackles, mallards, white pelicans) are thought to be indicative of exposure to lethal concentrations of endrin. Behavioral effects in bobwhite quail can be detected at levels of 0.1 mg endrin/kg diet. The critical NOAEL in brown pelican eggs was found to be <0.5 mg endrin/g ww of egg tissue.

The occurrence of convulsions is believed to be related to blood-brain permeability changes or to direct effects on the central nervous system. Although inhibition of membrane ATPases and mitochondrial ATPases from brain tissues have been detected, which were species-dependent, succinyl choline has prevented convulsions in all species tested. Concentrations of cytochrome P-450 in endrin-resistant animals (mice, pine voles) may be greater than in susceptible species (guinea pigs); gender may also be important. The conversion of endrin to anti- and syn-12-hydroxyendrins, and conversion of the syn-isomer to 12-ketoendrin may be dependent on the level and type of cytochrome P-450. The acute LD_{50} values for all these unconjugated metabolites are lower than for endrin itself. Lipid peroxidation may also play a role. The correlation of urinary D-glucaric acid with endrin exposure and the glucuronide of anti-12-hydroxyendrin in the urine in humans would support this hypothesis. D-glucaric acid has not been detected in human urine unless anti-12-hydroxyendrin levels in endrin equivalents were >0.13 mg/g creatinine.

Target organs appear to be the central nervous system in acute studies, and the liver, kidney and central nervous system in chronic studies.

The U.S. EPA has set an interim standard for endrin in finished drinking water of 0.0002 mg/ℓ (U.S. EPA, 1975). The present ambient water quality criteria for the protection of human health is 0.001 mg/ℓ and for the protection of both freshwater and saltwater aquatic life is 0.0023 μg/ℓ (U.S. EPA, 1980a). The World Health Organization (FAO/WHO, 1973) established as a guideline a maximum intake of 2 μg/kg/day, or 138.2 μg/day, for a 69.1 kg person. The proposed index Alimentarius Commission's maximum residue limit in wheat is 20 μg/kg (Bailey et al., 1982).

The threshold limit value (8-hour TLV/TWA) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) is 0.10 mg/m³ (0.10 mg/ℓ), with a short-time exposure limit (15 minutes) of 0.30 mg/m³ (ACGIH, 1982). Limits set by the Occupational Safety and Health Administration are the same as those recommended by the ACGIH (29 CFR 1910.1000).

The recommended 1-day health advisory (HA) for endrin in drinking water is 0.070 mg/ℓ for adults and 0.020 mg/ℓ for children. A NOAEL of 0.2 mg/kg bw/day based upon electroencephalographic changes in squirrel monkeys was used to derive the 1-day HAs. The estimated minimum dose of 0.25 mg/kg bw required to produce a single convulsion in humans provides additional support for these 1-day HAs.

The recommended 10-day HA for endrin is 0.018 mg/ℓ for adults and 0.0050 mg/ℓ for children. A NOAEL of 0.05 mg/kg bw/day based upon body weight changes in rats was used to derive the 10-day HAs.

The recommended AADI for chronic exposure to endrin is 0.0016 mg/ℓ. A NOAEL of 0.045 mg/kg bw/day based upon changes in heart and kidney weights in dogs was used to derive this AADI.

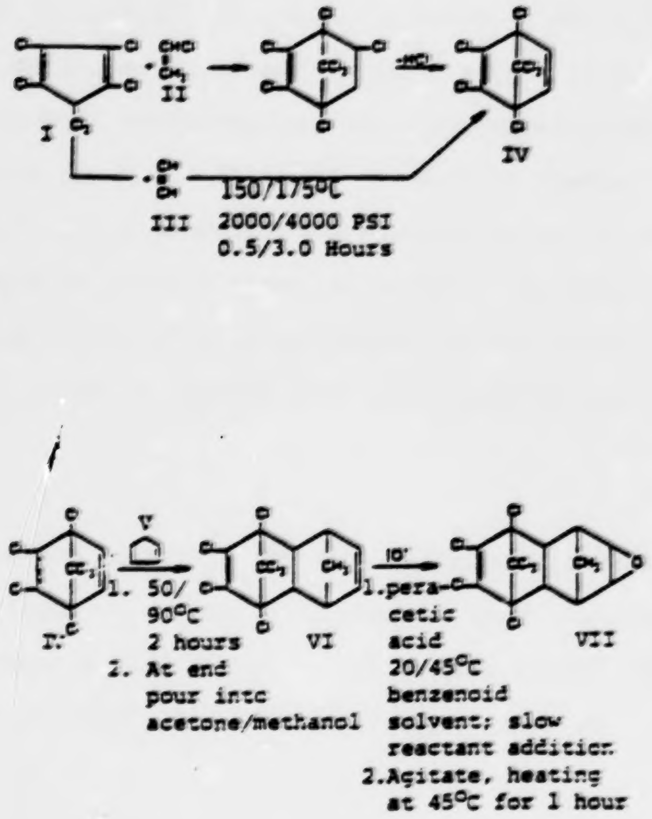
Insufficient information was reported to determine the carcinogenicity of endrin in either animals or humans. As a result, derivation of a quantitative risk estimate for cancer induction was not done.

II. PHYSICAL AND CHEMICAL PROPERTIES

Endrin is an aliphatic organochlorine cyclodiene pesticide, introduced as an insecticide into the United States in 1951. It has an empirical formula of $C_{12}H_8Cl_6O$ and a molecular weight of 380.93. It is produced by the epoxidation of a product (isodrin) obtained from the Diels-Alder reaction of hexachlorocycloheptadiene and cyclopentadiene (Brooks, 1974a). The major synthetic pathway is shown in Figure II-1. It has been manufactured in the United States by the Velsicol Chemical Corporation. Dipicolinic acid at levels of 0.5-500 ppm relative to endrin content is often utilized to stabilize solid endrin against decomposition by metallic impurities during the epoxidation step (Sittig, 1977). The synonyms of endrin are provided in Table II-1.

Chemical names and indexing terms for the major chemical degradation products of endrin are given in Table II-2, and for its major metabolites in Table II-3. The typical composition of technical grade endrin is provided in Table II-4. No other composition data were found in the literature searched.

The 1979 usage of endrin in the United States was ~175,500 kg (Anonymous, 1979). It was used as an insecticide on cotton and small grains and as a rodenticide in orchards (Eichers, 1980). With certain modifications endrin's limited use still continues although widespread resistance of many pests to it may account for further decline in its usage (Federal Register, 1979). Its use is still permitted in the cotton growing regions of western Oklahoma and western Texas, New Mexico, Arizona and California. Endrin is used on small grains to control the following insects: pale-western


CHCl
CH2
II
-HCl
IV
I
III
150/175°C
2000/4000 PSI
0.5/3.0 Hours
V
1. 50/
90°C
2 hours
2. At end
pour into
acetone/methanol
VI
10'
1.pera-
cetic
acid
20/45°C
benzenoid
solvent; slow
reactant addition
2.Agitate, heating
at 45°C for 1 hour
VII

I	hexachlorocyclopentadiene	II	monochloroethylene
III	acetylene	IV	hexachlorobicycloheptadiene adduct
V	cyclopentadiene	VI	isodrin
VII	endrin		

FIGURE II-1

The Major Industrial Synthetic Pathway for Endrin

(Modified from Sitting, 1977)

TABLE II-1

Nomenclature, Indexing Terms and Synonyms Currently Used for Endrin
(SANSS data base, June 1983)

CAS RN 72-20-8[a] Molecular formula: $C_{12}H_8Cl_6O$

2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,8,9,9-hexachloro-1a, 2,2a,3,-6,6a,7,7a-octahydro-(1a α,2 β,2a β,3 α, 6 α,6a β,7 β,7a α)-(9CI)[b]

1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,-6,7,8,8a-octahydro-endo,endo- (8CI)[c]

Compound 269

Endrex

Endricol

Endrin

Endrin isomer

Endrine (FRENCH)

Experimental Insecticide 269

EN 57 (VAN)

ENT 17,251

Hexachloroepoxyoctahydro-endo,endo-dimethanonaphthalene

Hexadrin

Mendrin

NCI-C00157

Oktanex

SD 3419

WLN: T E3 D5 C555 A A- FO KUTJ AG AG BG JG KG LG ENDO ENDO[d]

1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-endo-5,8-dimethanonaphthalene

1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo,endo-5,8-dimethanonaphthalene

---

[a] Chemical Abstracts Service Registry Number

[b] Ninth Collective Index, Chemical Abstracts

[c] Eighth Collective Index, Chemical Abstracts

[d] Wiswesser Line Notation

TABLE II-2

Chemical Information Related to Some Endrin Degradation Products

Common Chemical Names and Molecular Formula	CAS Indexing Term and CAS RN	Comment	Reference
Endrin aldehyde SD 7442 $C_{12}H_8Cl_6O$	1,2,4-Methenocyclopenta[cd]pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro-(1 α,2 β,2a β, 4 β,4a β, 5 β, 6a β,6b β,,7R)- 7421-93-4	Stereochemical configuration of aldehyde revised; structure confirmed with ^{13}C and ^{1}H nmr spectral data. Cpd is produced by thermal or photochemical rearrangement of endrin	Bird et al., 1978 Cox and McKinney, 1978
Endrin ketone δ-ketoendrin SD 2614 $C_{12}H_8Cl_6O$	2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b, 4,5,6,6,6a-hexachlorodecahydro-(2 α,3a β,3b β,4 β, 5 β, 6a β, 7 α,7a β,8R)-	Principal product of reaction of endrin with H_2SO_4	ApSimon et al., 1982
	53494-70-5	^{13}C nmr spectra	Cox and McKinney, 1978
No common chemical name 2,3,4,5,6-hexachloro-12-oxopentacyclo[5.4.1.$1^{8,11}$$0^{3,10}$.$0^{5,9}$]tridecane	6,2,3,5-[1,2]propanediyl[3]ylidene-2H-pentaleno[1,6-bc]furan, 2a,3,4,4,4a,6b-hexachlorooctahydro- 65956-39-0	Minor product (6-8%) of acid catalyzed rearrangement of endrin; single crystal X-ray diffraction and nmr data	ApSimon et al., 1982
Endrin alcohol $C_{12}H_8Cl_6O$	1,5,2,4-Ethanediylidenecyclopenta[cd]pentalen-1(2H)-ol, 2,2a,3,3,4,8-hexachlorooctahydro- 33058-12-7	^{13}C nmr spectra	Cox and McKinney, 1978

TABLE II-3

CAS Indexing Terms and CAS RN for Endrin Metabolites (from CHEMLINE, 1983)

Common Chemical Names and Molecular Formula	CAS Indexing Term and CAS RN
12-Ketoendrin WL 41435 $C_{12}H_6Cl_6O_2$	2,7:3,6-Dimethanonaphth(2,3-b)oxiren-8-one, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-,(1a α,2 β,2a β,3 α,6 α,6a β,7 β,7a α)- (9CI) 1,4:5,8-Dimethanonaphthalen-9-one, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro- (8CI) 28548-08-5
anti-12-Hydroxyendrin WL 41434 $C_{12}H_8Cl_6O_2$	2,7:3,6-Dimethanonaphth(2,3-b)oxiren-8-ol, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1a α,2 β,2a β,3 α,6 α,6a β,7 β,7a α)- (9CI) 1,4:5,8-Dimethanonaphthalen-9-ol, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro- (8CI) 49748-76-7
3-Hydroxyendrin $C_{12}H_8Cl_6O_2$	2,7:3,6-Dimethanonaphth(2,3-b)oxiren-2(1aH)-ol, 3,4,5,6,9,9-hexachloro-2a,3,6,6a,7,7a-hexahydro-, (1a α,2 α,2a β,3 α,6 α,6a β,7 β,7a α)- (9CI) 57378-25-3

CI = Collective Index

TABLE II-4

Typical Composition of Technical Grade Endrin*

Component	% (by weight)
Endrin	96.6
HEOD	0.42
HHDN	0.03
Isodrin	0.79
Heptachloronorbornadiene	0.03
Heptachloronorbornene	0.08
δ-Ketoendrin	1.57
1,2,3,4,5-pentachloro-7-oxo-1,4,5,6-tetrahydro-1,4-methanobenzene	0.09
Endrin aldehyde	<0.05
Acidity (as HCl)	0.18
Unidentified	0.12
Water content	<0.1
Xylene insoluble residue	<0.5

*Adapted from Brooks, 1974a

cutworm, army cutworm, and grasshoppers. Additionally, it is used to control the sugarcane beetle and pine voles in the eastern United States and western meadow voles in the western United States and in the treatment of conifer seeds (Federal Register, 1979). It is also used as bird perch toxicant (Hadler, 1982). Endrin has been generally coformulated to minimize its tendency to decompose in some common formulation carriers (Brooks, 1974a). Often, up to 15% (w/w) of hexamethylene tetramine has been used for this purpose. Endrin is often coformulated with methyl parathion in emulsifiable concentrates. A selected list of pesticidal mixtures in which endrin is not the only pesticidal component is provided in Table II-5. Pure endrin appears to decompose above 245°C (Metcalf, 1981), although technical grade endrin (>92% endrin) decomposes above 200°C (Brooks, 1974a).

Endrin is soluble in nonpolar solvents. The solubility of pure endrin (in g/100 mℓ at 25°C) is as follows: acetone, 17; benzene, 13.8; carbon tetrachloride, 3.5; xylene, 18.3; and water, 0.000023 (Metcalf, 1981). The equivalent solubilities for technical grade endrin (55-57% chlorine content) is as follows: acetone, 31; benzene, 51; carbon tetrachloride, 51; isopropanol, 3; methanol, 2; methyl ethyl ketone, 40; toluene, 74; and xylene, 55 (Brooks, 1974a). The specific gravity of the technical grade compound is 1.7 at 20°C. The vapor pressure of technical grade endrin is 2.7×10^{-7} mm Hg at 25°C (Brooks, 1974a). Endrin appears to obey a Freundlich adsorption isotherm in the presence of an activated carbon (200/400 mesh) aqueous slurry (U.S. EPA, 1980b). Kenaga (1980) has provided the following physical constants for endrin at 25°C: water solubility, 0.024 ppm (compare the 0.23 ppm value above); octanol/water partition coefficient, 2.18×10^{5}; and a calculated organic soil adsorption constant of 3.4×10^{4}.

TABLE II-5

Some Pesticide Mixtures in which Endrin is not the Only Pesticide
(Chemname, 1983)*

CAS Registry Number	Component CAS Registry Numbers	Component Chemical Names (endrin chemical name omitted)	Synonyms
53858-08-5	(50-29-3, 72-20-8, 298-00-0)	1,1'-(2,2,2-trichloroethylidene)bis(4-chlorobenzene) Phosphorothioic acid, O,O-dimethyl-O-(4-nitrophenyl) ester	DDT-endrin-methyl parathion mixture
58939-75-6	(72-20-8, 121-75-5)	Butanedioic acid, ((dimethoxyphosphinothioyl)thio)-, diethyl ester	Malathion-endrin mixture
59928-82-4	(72-20-8, 947-02-4)	Phosphoramidic acid, 1,3-dithiolan-2-ylidene-, diethyl ester	Cyolane-endrin mixture
64034-60-2	(57-13-6, 72-20-8)	urea	Endrin-urea mixture
65437-77-6	(72-20-8, 7704-34-9)	2,7:3,6-Dimethanonaphth(2,3-b)oxirene	Endrin-sulfur mixture
8017-73-0	(60-57-1, 309-00-2) (72-20-8)	2,7:3,6-Dimethanonaphth(2,3-b)oxirene, mixture with (1.α.,4.α.,4a.β.,5.α.,8.α.,8a.β.)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene	Lepit; Aldrin-dieldrin mixture; Binarin
8066-55-5	(72-20-8, 640-15-3)	Phosphorodithioic acid, S-(2-(ethylthio)ethyl)-O,O-dimethyl ester, mixture	Veldrin EE 922:Veldrin; Ekadrin; Thiometon-endrin mixture

TABLE II-5 (cont.)

CAS Registry Number	Component CAS Registry Numbers	Component Chemical Names (endrin chemical name omitted)	Synonyms
8075-40-9	(72-20-8, 309-00-2)	2,7:3,6-Dimethanonaphth(2,3-b)oxirene, mixture with (1.α.,4.α.,4a.β.,5.α., 8.α.,8a.β)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene	Aldrin mixture with endrin; Endional; Mauxan; Tricotin
37247-09-9	(50-29-3, 72-20-8)	2,7:3,6-Dimethanonaphth(2,3-b)oxirene, mixture with 1,1'-(2,2,2-trichloroethylidene)bis(4-chlorobenzene)	DDT-endrin mixture; Endrin-DDT mixture
37262-64-9	(72-20-8, 298-00-0)	Phosphorothioic acid, O,O-dimethyl-O-(4-nitrophenyl) ester, mixture	Endrin-methyl parathion mixture
37338-61-7	(72-20-8, 141-66-2)	Phosphoric acid, 3-(dimethylamino)-1-methyl-3-oxo-1-propenyl dimethyl ester, mixture	Endrin-bidrin; Endrin-bidrin mixture; Endrin-dicrotophos
51602-20-1	(72-20-8, 21609-90-5)	Phosphonothioic acid, phenyl-, O-(4-bromo-2,5-dichlorophenyl) O-methyl ester, mixture	Endrin-leptophos mixture
59928-83-5	(72-20-8, 950-10-7)	Phosphoramidic acid, (4-methyl-1,3-dithiolan-2-ylidene-, diethyl ester, mixture	
61912-61-6	(72-20-8, 6923-22-4)	Phosphoric acid, dimethyl-1-methyl-3-(methylamino)-3-oxo-1-propenyl ester, (E)-, mixture	

TABLE II-5 (cont.)

CAS Registry Number	Component CAS Registry Numbers	Component Chemical Names (endrin chemical name omitted)	Synonyms
62588-93-6	(56-38-2, 72-20-8)	Phosphorothioic acid, 0,0-diethyl-0-(4-nitrophenyl) ester, mixture	
62815-24-1	(72-20-8, 13171-21-6)	Phosphoric acid, 2-chloro-3-(diethylamino)-1-methyl-3-oxo-1-propenyl dimethyl ester, mixture	
63952-62-5	(72-20-8, 16752-77-5)	Ethanimidothioic acid, N-(((methylamino)carbonyl)oxy)-, methyl ester, mixture	
63952-72-7	(72-20-8, 2104-64-5)	Phosphonothioic acid, phenyl-, 0-ethyl, 0-(4-nitrophenyl) ester, mixture	
65437-77-6	(72-20-8, 7704-34-9)	2,7:3,6-Dimethanonaphth(2,3-b)oxirene, mixture with sulfur	Endrin-sulfur mixture

*Dialog Information Services, Inc.

Spectroscopic Properties

Since endrin is not aromatic and does not contain conjugated double bonds, it has a $\Sigma\frac{1}{1}$ of $148\%^{-1}$ cm^{-1} at the λ_{max} at 225 nm (Tewari and Sharma, 1978). Thus ultraviolet/visible spectroscopy would be neither sensitive nor useful analytically.

Infrared analysis is practical when utilizing the peak at 11.76 μm and baseline points at 11.50 and 11.97 μm (Brooks, 1974b). The mass spectrum is diagnostic (Safe and Hutzinger, 1973a). The molecular ion (m/e 378) is small with successive losses of Cl (m/e 343, 308). These latter peaks are intense enough to be utilized for specific ion monitoring purposes. A Retro Diels-Alder process also occurs. Chemical ionization mass spectrometry has also been performed (Safe and Hutzinger, 1973b). Cox and McKinney (1978) measured the ^{13}C-NMR spectra of endrin, endrin aldehyde, endrin ketone and endrin alcohol.

Chemistry

Endrin decomposes at temperatures above 200°C or when stored for long periods, with endrin aldehyde and a pentacyclic aldehyde as decomposition products (Brooks, 1974a). This process is important for gas chromatographic analysis in metal columns (Phillips et al., 1962). Endrin undergoes epoxide ring opening and rearrangement in the presence of acid or of metal catalysts, i.e., iron compounds (Brooks, 1974a). Endrin ketone is the principal product of acid decomposition (Apsimon et al., 1982). Endrin can undergo the usual addition reactions, and also complex transannular rearrangements.

When exposed to wavelengths of 253.7 and 300 nm and to sunlight, endrin in hexane and cyclohexane decomposes to the following half-cage ketone, 1,8-exo-9,11,11-pentachloropentacyclo[6.2.1.$1^{3,6}$.$0^{2,7}$.$0^{4,10}$]dodecan-5-one, with 60% conversion in 8 hours. This product has been identified in environmental samples (Zabik et al., 1971). Photorearrangement is possible above 300 nm in the presence of appropriate photosensitizers, e.g., silica gel (Ivie and Casida, 1971a) and rotenone on bean leaves (Ivie and Casida, 1971b). For the latter case but not the former, endrin ketone and endrin aldehyde are the major products. The nomenclature, CAS indexing terms and CAS RNs for the major degradation products are given in Table II-2. The reaction of acidified zinc dust with endrin has been suggested as a degradation procedure in the field (Butler et al., 1981).

Analytical Methods

The most recent analytical methods for endrin in animal tissues and fluids are summarized in Table II-6. Most of the methods involve extraction to separate endrin from its matrix, then cleanup or extraction before electron capture gas chromatography (EC/GC) or gas chromatography/mass spectrometry (GC/MS). Heating above 200°C or acidification in any of the analytical steps will cause degradation of the endrin as described in the chemistry section. This may be the reason for the highly variable recoveries quoted in the literature or for residues not being detected in the majority of studies. For water analysis, if waters are already acidic, probably most of the endrin will have been degraded already to endrin ketone. At 25°C and pH 2 water, endrin recovery is 23%; at pH 7-10 its recovery is 88% (Millar et al., 1981). At 4°C at pH 2, however, the recovery is 92%; 85% of endrin

TABLE II-6

Analytical Methods for Determining Endrin or Endrin Transformation Products in Tissues or Animal Fluids

Human Tissue or Fluid	Compound Determined	Method	Reference
Human urine	*anti*-12-hydroxyendrin and β-glucuronide conjugate	oxidation of conjugate with meta periodate hydrolysis;hexane extraction/EC/GC	Baldwin and Hutson, 1980
Human adipose tissue	endrin	hexane extraction/gel permeation chromatography cleanup/EC/GC (100% recovery at 3.2 ppm)	MacLeod et al., 1982
		hexane extraction/gel permeation chromatography cleanup/EC/GC (105% recovery)	Tessari et al., 1980
Cow milk	endrin	extractions/Florisil cleanup/EC/GC (80% recovery; detection limit 0.5 ppb)	Frank et al., 1979
Bird brain	endrin	sodium sulfate/milling/soxhlet extraction (diethylether and petroleum ether)/EC/GC (70±6% recovery; detection limit 0.05 ppm for a 1 g sample)	Ludke, 1976

aldehyde is recovered at pH 2, 7 or 10 at 4° or 25°C but is degraded in the presence of chlorine at pH 10 (Millar et al., 1981). Carbopack B columns have also been used to concentrate 8 ppb endrin from water (Mangani et al., 1981), as have XAD-2 resins (Rees and Au, 1979). A standard NIOSH method is available for monitoring airborne endrin in the personal sampling mode (solid sorbent/battery powered pumps) (Taylor, 1980).

Summary

Endrin is an aliphatic organochlorine insecticide with a molecular weight of 380.93, water solubility of 0.024 ppm, specific gravity of 1.7 at 20°C, vapor pressure of 2.7×10^{-7} mm Hg at 25°C and an octanol water partition coefficient of 2.18×10^{5}. It is used predominantly to control cutworms and grasshoppers, but has also been used as a denticide in the control of eastern pine voles and western meadow voles.

Endrin decomposes at temperatures >200°C into endrin aldehyde and a pentacyclic aldehyde. Acids or metals (iron) will also decompose endrin into endrin ketones and aldehydes. Following extraction methods endrin levels in tissue and water analysis may be determined by EC/GC or GC/MS techniques.

III. TOXICOKINETICS

This section refers only to data relevant to warm-blooded vertebrates.

Absorption

Endrin is absorbed through the skin, by the lungs and by the gut (U.S. EPA, 1980a). Rates of absorption have not been documented. That absorption does occur is demonstrated by the data in Table III-1 concerning residue levels and biological effects after exposure.

Oral. Wild and domestic animals that have absorbed endrin through ingestion of treated foliage can show residues in fat, blood and milk (see Table III-1). Several poisoning incidents have occurred through animal feeds (Long et al., 1961; Terriere et al., 1958; Kiigemagi et al., 1958; Hunter et al., 1960; U.S. EPA, 1980a). For an early review of poisoning incidents see Brooks (1969).

Animals and birds at the top of food chains as well as humans may be particularly affected by the oral route of exposure if the chemical or its metabolites bioaccumulate. The weighted average BCF for endrin is 3970 for the edible portion of all freshwater and estuarine fish and shellfish consumed by United States residents (U.S. EPA, 1980a).

Humans have ingested endrin-treated agricultural products (Carey et al., 1979) as well as meat from domesticated and wild animals, birds and fish. Poisoning of humans after accidental contamination of food has been attributed to doses as low as 0.2 mg/kg bw (U.S. EPA, 1980a).

TABLE III-1

Evidence of Absorption Using Residue and Biological Effect Data

Route of Absorption	Applied Dose	Residues	Biological Effects	Reference
Oral	not known on pasture	up to 24 µg/g fat, 6.4-14 µg/g after 42 days	Not reported	Long et al., 1961
	510 mg over 30 days to pigs	up to 2 µg/g fat	Not reported	Hunter et al., 1960
	20 mg/day/cow	up to 0.25 µg/g milk	Not reported	U.S. EPA, 1980a
	>0.2 mg/kg bw in humans	up to 10 µg/g blood 400 µg/g fat	Poisoning symptoms in humans; convulsions	U.S. EPA, 1980a Hayes, 1963 Coble et al., 1967 Weeks, 1967 Curley et al., 1970 Tewari and Sharma, 1978
Inhalation/ dermal	"grossly exposed" humans	residues >1 µg/g blood	Convulsions at >0.2 mg/kg bw	Jager, 1970a,c
	animal mortality data			
Dermal	Carworth Farm Strain E (CFE) rats in acute dose response experiments	not reported	Ratio of dermal to acute oral LD_{50} for 20% emulsifiable concentrate is 1.6; and for 2% dust is 13	Muir, 1968

Inhalation

Since the vapor pressure of technical endrin is 2.7×10^{-7} mm Hg at 21°C (see Chapter II), this is equivalent to a vapor density of 5.5 $\mu g/m^3$ of air. Consideration of endrin's inhalation hazard to humans led the American Conference of Governmental Industrial Hygienists (ACGIH, 1982) to set the threshold limit value, 8-hour time weighted average (TLV-TWA), to be 0.10 mg/m^3 with a short-term exposure limit (STEL) for 15 minutes of 0.30 mg/m^3 (skin). The OSHA standard based on the 1968 ACGIH TLV is 0.10 mg/m^3 (skin) (NIOSH, 1978). Dermal absorption occurs concurrently with air exposure as denoted by the "skin" designation.

Few blood residues have been found in endrin-exposed workers, except in those grossly exposed (Jager, 1970a). The absence of residues may imply fast metabolism or negligible absorption. In this case, fast metabolism is responsible.

Dermal

The most significant dermal exposures to endrin in the occupational environment have occurred during field applications (Wolfe et al., 1963, 1967). Unfortunately, no residues have been reported to confirm absorption. Both inhalation and dermal exposure have occurred during endrin manufacture and distribution, but only grossly exposed workers have ever shown residues. Nevertheless, convulsions have been reported in such workers (Jager, 1970a,c).

The dermal acute LD_{50} value for male CFE strain rats is 1.6 times that for the oral acute value (diet) when the rats were exposed to a 20% emulsifiable concentrate (Muir, 1968). Similarly, for exposure to a 20% field strength dust, the ratio was 13 (Muir, 1968), illustrating the importance of the carrier in dermal absorption (see Chapter V). Such data demonstrate that endrin is absorbed through the skin of rats and is probably also absorbed through human skin, as the "skin" designation for the ACGIH TLV-TWA implies.

Distribution and Metabolism

In contrast to its stereoisomer dieldrin, endrin is rapidly metabolized in mammals and the metabolites are also quickly eliminated. Thus, the distribution of endrin itself in tissues even after high doses may be below detection limits. Under such conditions, distribution studies with radiolabeled endrin may not reflect endrin distribution, but that of its metabolites. However at very high doses, e.g. human poisoning cases, gross occupational exposures or in suicide cases, endrin can be detected in tissues. Endrin appears to accumulate more in birds (excluding chickens) than in mammals.

Distribution in Human Tissues. Endrin is a relatively nonpersistent pesticide in humans. Measurable levels of endrin have not been detected in adipose tissue (Kutz et al., 1979) or the blood of the general population, even in those areas where endrin was used extensively, such as India or the lower Mississippi delta area (Brooks, 1974a). Endrin also has not been found in the blood of workers who manufacture or formulate endrin (Hayes and Curley, 1968; Baldwin and Hutson, 1980) except in the case of very high levels of exposure (Jager, 1970a).

Measurable tissue endrin concentrations are reached in cases of acute poisoning. The time of sample collection is important to these measurements, as endrin residues decline rapidly in tissues after cessation of exposure. Endrin concentrations as high as 10 mg/kg in blood and 400 mg/kg in fat have been reported (Hayes, 1963). In an incident involving three acutely poisoned humans in the United Arab Republic in 1967, no endrin was detected (<4 μg/kg) in cerebrospinal fluid (Coble et al., 1967). The serum, 30 minutes after one patient's convulsion, contained 53 ng endrin/mℓ. After 20 hours the serum concentration was 38 ng/mℓ, and after a further 10 hours, 21 ng/mℓ. In the same patient, the endrin level in a 24-hour urine sample after convulsion was 20 ng/mℓ. Levels of endrin much lower than 10 mg/kg tissue were obtained in autopsies of 26 Saudi Arabians poisoned by endrin-contaminated bread (Weeks, 1967; Curley et al., 1970). In the same incident 874 people were hospitalized, and another 500-750 people were also exposed. Blood from the hospitalized patients contained 7-32 ng endrin/mℓ blood. Blood and urine samples taken from patients 29-31 days after the episode contained no detectable amounts of endrin. Summary data are given in Table III-2.

Tewari and Sharma (1978) studied the concentration of endrin by TLC/ultraviolet spectrophotometry of autopsy materials of eleven cases of fatal poisoning. These results are also summarized in Table III-2. High concentrations were found in fat-containing tissues, even for a time to death of 6 hours. There was some evidence to suggest that endrin in combination with a fatty carrier, such as milk caused death faster than when ingested with solid food. The levels quoted may be in error as endrin, 12-hydroxyendrin or 12-ketoendrin were not separated.

Measurable tissue endrin concentrations are reached in cases of acute poisoning. The time of sample collection is important to these measurements, as endrin residues decline rapidly in tissues after cessation of exposure. Endrin concentrations as high as 10 mg/kg in blood and 400 mg/kg in fat have been reported (Hayes, 1963). In an incident involving three acutely poisoned humans in the United Arab Republic in 1967, no endrin was detected (<4 μg/kg) in cerebrospinal fluid (Coble et al., 1967). The serum, 30 minutes after one patient's convulsion, contained 53 ng endrin/mℓ. After 20 hours the concentration was 38, and after a further 10 hours, 21 ng/mℓ serum. In the same patient, the endrin level in the 24-hour urine after convulsion was 20 ng/mℓ. Levels of endrin much lower than 10 mg/kg tissue were obtained in autopsies of 26 Saudi Arabians poisoned by endrin-contaminated bread (Weeks, 1967; Curley et al., 1970). In the same incident 874 people were hospitalized, and another 500-750 people were also exposed. Blood from the hospitalized patients contained 7-32 ng endrin/mℓ blood. Blood and urine samples taken from patients 29-31 days after the episode contained no detectable amounts of endrin. Summary data are given in Table III-2.

Tewari and Sharma (1978) studied the concentration of endrin by TLC/ultraviolet spectrophotometry of autopsy materials of eleven cases of fatal poisoning. These results are also summarized in Table III-2. High concentrations were found in fat-containing tissues, even for a time to death of 6 hours. There was some evidence to suggest that endrin in combination with a fatty carrier, such as milk or lipid, caused death faster than when ingested with solid food. The levels quoted may be in error as endrin, 12-hydroxyendrin or 12-ketoendrin were not separated.

TABLE III-2

Endrin Concentrations Found in Victims of Endrin Poisoning

Sample	Endrin Concentrations (mg/kg)	
	in Saudi Arabia[a]	in suicides[b]
Blood	0.007-0.032[c]	4.3-8.5
Urine	0.004-0.007[c]	2.5-5.5
Vomitus	5.24	32.5-81.2
Tissues (autopsy) from:		
Stomach	0.16	10.4-145
Liver	0.685	9.4-200
Kidney	0.116	7.5-51.7
Spleen	NA	2.4-21.7
Heart	NA	5.6-19.9
Lung	NA	3.8-10.8
Intestine	NA	13.1-660

[a] Curley, et al., 1970 (includes first and third Dohar outbreaks and Hofuf outbreak)

[b] Tewari and Sharma, 1978 (11 suicides)

[c] On day of onset

NA = not analyzed

Little is still known of the distribution and persistence of endrin metabolites in human tissues. Baldwin and Hutson (1980) were unable to detect anti-12-hydroxyendrin or 12-ketoendrin in the blood of endrin workers at a Shell manufacturing plant in England. The method used had a detection limit of 2 ng/mℓ for both compounds.

By analogy with observations made in experimental animals, it may be speculated that endrin and its metabolites are rapidly eliminated. It is noteworthy in this regard that recovery from an acute poisoning episode is rapid, on the order of a day (Davies and Lewis, 1956), so that if toxic metabolites are formed in humans they are not persistent.

Distribution in Animal Tissues.

Birds -- Researchers agree that endrin is absorbed from the avian gut and stored in various body tissues by both wild and domestic species (Terriere et al., 1959; Reichel et al., 1969).

After absorption of endrin, residues have been reported to be distributed among liver, brain, adipose, eggs, breast muscle and gonadal tissues. Adipose tissues generally contained the highest concentration (Gregory, 1970; Terriere et al., 1959), while brain tissues usually contained the lowest (Reichel et al., 1969).

Terriere et al. (1959) examined the tissues and eggs of chickens exposed to levels of 0.1, 0.25 and 0.75 mg endrin/kg feed. In one experiment, 1-month-old male Delaware X New Hampshire chicks were fed the various endrin levels for 6 weeks and then sacrificed, while 6-month-old White Leghorn pullets were exposed to the endrin-fortified feed for 8 weeks and were returned to the basal diet for 4 additional weeks. A repeat of the male chick experiment using New Hampshire X Delaware chicks was also performed. In all endrin exposures, the amount of adipose tissue was found to be meager even though weight gain and feed consumption appeared to be normal. At a level of 0.25 mg/kg feed or higher, definite deposition of endrin in the egg tissue occurred within 2-4 weeks after exposure had ceased. Accumulation of endrin in adipose tissue was found in both experimental groups with even the lowest dietary level showing evidence of deposition. Analysis of breast and tibia tissue revealed endrin deposition at both the 0.25 and 0.75 mg/kg feed intake levels.

The fat tissue of the plain chachalacas, Ortalis vetula, was analyzed by Marion (1976) for pesticide residues during 1971 and 1972. In four different study areas 24 birds had an average endrin residue of 0.13±0.52 mg/kg weight. There was no evidence that these birds died of endrin exposure. Only 8 of the 24 birds sampled contained detectable endrin residues.

The percentage of the dose retained by bobwhite quail appears to be dependent upon administration time and dose according to Gregory et al. (1972). Analyses of whole birds fed equal doses of endrin-contaminated beans or beetles revealed retention of ~16% of the total acute dose ingested, while 21% of the total chronic dose was retained. The residues found in the body tissues during the acute and chronic experiments differed, but not consistently. The average endrin content in adipose tissues in the acute dosage group was 0.014±0.002 mg/kg ww, as compared with 0.010±0.001 mg/kg found in the chronic dosage group. Gonadal tissues from both groups contained traces of endrin, while the concentration of liver residues in the chronic test was 0.007 mg/kg and in the acute test, 0.004 mg/kg.

Baldwin et al. (1976) fed 10 Sykes Hybrid III hens (~2 kg) 0.13 mg endrin/kg diet by capsule over 148 days. At day 148, the levels of endrin and 12-ketoendrin were measured in muscle, liver, kidney and fat (Table III-3). Levels of 12-ketoendrin, deltaketoendrin, anti- and syn-12-hydroxy-endrins were below detection. The distribution of ^{14}C-endrin provided at 0.3 μCi/day for 148 days is given in Table III-4 for day 148. These results for radioactivity essentially are for endrin distribution itself, as supported by the data in Table III-3.

Ludke (1976) fed 20 bobwhite quail diets containing 10 ppm chlordane for a 10-week period followed immediately by 10 ppm endrin in the diet for 10 weeks; 20 other quail received 10 ppm endrin in the diet only. After another 9-10 days on an uncontaminated diet, the survivors were sacrificed. All birds were found to have lost weight. Mortality from the endrin diet was associated with as little as 0.34 mg/kg ww in the brain of the quail.

Endrin has also been detected (0-4% occurrence) in the wings of black ducks (*Anas rubripes*) at 0.01 mg/kg ww, and of adult mallards (*Anas platyrhynchos*) up to 0.02 mg/kg during the 1976-1977 National Pesticide Monitoring Program (White, 1979).

Blus et al. (1979) found endrin residues in all of the eggs of brown pelicans from Louisiana, many of which had lethal levels of residue in their brains. The year/number/levels in eggs were as follows: 1971, 3, 0.08-0.12 mg/kg ww; 1972, 12, 0.11-0.29; 1973, 21, 0.03-0.46; 1974, 25, ND-0.73; 1975, 30, 0.29-1.06; 1976, 25, ND-1.47.

TABLE III-3

Distribution of Endrin and 12-Ketoendrin at Day 148 in Sykes Hybrid III Hens (2 kg initially) Fed 0.13 mg/kg Diet by Capsule*

Tissue	Concentration (mg compound/kg ww)	
	Endrin	12-Ketoendrin
Breast meat	<0.0032-0.0013	<0.002
Leg meat	0.017-0.095	<0.003
Liver	0.013-0.20	<0.0006
Kidney	0.035-0.13	<0.03
Fat	0.32-1.21	<0.0004

*Source: Baldwin et al., 1976

TABLE III-4

Radioactivity in Tissues of Five Hens After a 148-Day Period of Treatment with 0.3 μCi/Day (as capsules)*

Tissue	Radioactive Residues (mg endrin equivalent/kg ww)
Breast meat	0.008-0.011
Leg meat	0.008-0.030
Fat	0.50-1.28
Liver	0.07-1.06
Kidney	0.13-0.23
Brain	0.017-0.050
Sciatic nerve	0.096-0.64
Bone marrow	0.14-0.58
Skin	0.13-0.39
Feathers	0.005-0.024

*Source: Baldwin et al., 1976

In September 1978, ducks in Montana were found to contain up to 1.2 mg/kg ww endrin in their fat resulting from endrin applied on wheat crops to destroy an infestation of Army cutworms (Anonymous, 1979).

Table III-5 shows some typical residue levels found since 1977 in wild and laboratory birds known to be exposed to endrin. These data illustrate that endrin is absorbed and then distributed throughout the body. No 12-ketoendrin was detected in the tissues of wild or domestic birds, unless the birds had ingested endrin-killed fauna (Stickel et al., 1979a). The connection of brain residues with lethality is discussed in Chapter V.

Mammals -- Little is known of the transport and distribution of endrin in mammals. No evidence of storage in any particular tissue or organ, other than fat, has been found. Residues of endrin ranging from 0.001-23.7 mg/kg ww, however, have been detected in a variety of mammalian tissues.

Brooks (1969) reviewed studies showing that steers, lambs and hogs receiving 0.1 mg endrin/kg diet for 12 weeks had little tendency to deposit endrin in body tissues. Continuous feeding of endrin at levels up to 2 mg/kg diet resulted in a maximum body fat concentration of 1 mg endrin/kg ww. Cattle with only ambient environmental endrin exposure were analyzed for the presence of endrin residues in their tissues by the U.S. Department of Agriculture in 1967 (Spaulding, 1972). Of the 2785 animals studied, 2783 contained no endrin residues; one animal contained between 0.01 and 0.1 mg endrin/kg fat, and another contained between 0.11 and 0.5 mg/kg fat.

TABLE III-5

Endrin Distribution in Birds in the Post-1978 Literature

Species	Exposure Type	Tissue	Concentration (number) (mg/kg ww)	Reference
Heron (wild)	NR	carcass[a]	0.10-0.86 in MN (9) 0.19-0.22 in VA (3) 0.20 in FL (1) 0.30-0.42 in CA (2) 0.19-0.60 in WI (4)	Ohlendorf et al., 1981
Kestrel (wild)	NR	carcass	0.42-0.63 (2)[b]	Stickel et al., 1979b
		GI tract	0.09-0.17	
Broadwinged hawk (wild)	NR	carcass	0.07	Stickel et al., 1979b
White pelican (dead) (wild)	NR	carcass	1.1[b]	
		brain	0.74[b]	Stickel et al., 1979a
Pelican (wild)	NR	brain	0.46-2.7 (21)	Stickel et al., 1979a
Bobwhite quail	5.8 μg/kg fed/day/bird	brain	0.047-0.093 at 138 days	Kreitzer, 1980
Bullfinch	0.15% endrin (48 hours)	liver	0.56-3.65 (M/F)	Feare et al., 1978
	0.0375% endrin (24 hours) (via pear buds)	liver	0.19-1.28 (F)	
Grackles	10 mg/kg diet	carcass	0.67-1.6[b] (8)	Stickel et al., 1979a
		brain	1.1-2.2[b]	

TABLE III-5 (cont.)

Species	Exposure Type	Tissue	Concentration (number) (mg/kg ww)	Reference
Mallard	10 mg/kg diet (26 days)	carcass	1.4-1.9[b] at day 26 (2)	Stickel et al., 1979a
		brain	0.54-0.77[b]	
		liver	1.1-1.9	
Quail (dead)	50 mg/kg diet	carcass	1.1 (M)[b] on day 14-20 (4) 1.0 (F)[b] on days 13-15	Stickel et al., 1979a
Eagle (dead)	20 mg/kg diet	carcass	1.5 (F)	Stickel et al., 1979b
		muscle	0.63 (M)	
		brain	0.92-1.2 (M/F)	
Eagle (wild)	NR	carcass	0.5-2.5 (M)	Stickel et al., 1979b
		brain	0.71-1.2 (M)	

[a] After head, skin, feet, wingtips and GI tract were removed

[b] 12-Ketoendrin was below the detection limit

NR = Not reported

By 1971, however, similar testing revealed that endrin incidence in tissues was increasing. Of 2403 cattle tested, 42 had levels of 0.01-0.1 mg endrin/kg fat (Spaulding, 1972).

Long et al. (1961) reported high levels of storage in the adipose tissue of six lambs using a dechlorination method of analysis. Higher levels were detected in the internal fat surrounding the stomach and thoracic cavity than in external fat deposits. Lambs were allowed to graze for 55 days on pastures treated with 2% endrin granules, applied six times in May and June at a rate of ~1.1 kg endrin/acre. The lambs were then transferred to untreated pasture, and endrin in fat was measured after 0, 14 and 42 days. At the start of grazing in untreated pastures, lambs had 18.3-23.4 mg endrin/kg internal fat and 11.5-14.0 mg/kg external fat. After 14 days, endrin levels were surprisingly higher, with 20.3-23.7 mg/kg internal fat, and 14.6-20.1 mg/kg external fat. Some loss did occur after 42 days. Internal fat levels dropped to concentrations of 8.9-13.8 mg/kg fat, and external fat contained only 6.4-11.0 mg/kg. These findings seem to contradict later reports by Brooks (1969) of no storage and no retention. In the Long et al. (1961) study, however, much higher levels of endrin were fed to younger animals; younger animals have relatively more fat than adults. In addition the lambs initially were in "poor condition." Sharma and Gautam (1971) detected endrin residues in the brain and liver tissue of calves. In the domestic dog endrin was detected in the abdominal viscera (Reins et al., 1966) as well as in fat (Richardson et al., 1967).

Richardson et al. (1967), using three 9-month-old beagle dogs fed 0.1 mg endrin/kg bw/day and two control animals fed uncontaminated diet over the 128-day feeding period, found that endrin in jugular vein blood in each dog reached a plateau at 3-8 mg/kg after 2 days of feeding. The distribution of endrin in tissues after 128 days of feeding is provided in Table III-6. Only the levels in fat were related to levels of endrin in blood. In contrast, administered dieldrin accumulated in the blood after 114-121 days. Rats dosed at 8 μg of ^{14}C-endrin/day by the oral route achieved a steady-state in the blood in 9-10 days (Brooks, 1969), but the label was quickly eliminated after cessation of exposure.

Korte (1967) showed that conversion of endrin to metabolites was not dependent on enterobacteria but occurred in the liver, and in 1970 found that the steady-state storage level after 6 days for female rats dosed at 0.4 mg ^{14}C-endrin/kg diet (16, 64 and 128 μg endrin/kg/bw) was about twice that for males dosed similarly (27% vs. 14%, respectively) (Korte et al., 1970). After i.v. injection of 200 μg ^{14}C-endrin/kg in two doses, male rats retained 5.2% and females 12.1% after 24 hours. This illustrated that the results for different genders were probably not due to gender-dependent absorption variability. Baldwin et al. (1970) also found that concentrations of endrin metabolites in female rats were dependent on the duration of feeding (4 mg/endrin/kg feed over several weeks), whereas those in males were not. Walsh and Fink (1972) gave 5 Carworth Farm No. 1 adult mice 5 mg ^{14}C-endrin/kg bw by i.v. using DMSO as a vehicle. After 10 minutes the radioactivity distribution was as shown in Table III-7. Endrin was as penetrative to the blood-brain barrier as dieldrin; no endrin was found in the bile up to 2 hours after administration.

TABLE III-6

Distribution of Endrin and 12-Ketoendrin in Experimental Animals

Animal (Number)	Dose (mg endrin/kg bw)	Tissue	Concentration (mg compound/kg tissue)		Reference
			Endrin	12-Ketoendrin	
Beagle dog (3) (9-month-old)	0.1 mg/kg bw/day over 128 days	spleen[a]	0.12-2.62		Richardson et al., 1967
		fat[a]	250-760		
		muscle[a]	120-310		
		pancreas[a]	87-280		
		heart[a]	125-170		
		liver[a]	77-84		
		kidney center[a]	38-82		
		blood[a]	1-8		
CFE rat (6) (female, 200-250 g)	2.5 in arachis oil	fat[b]	5.49±0.32	2.27±0.67	Hutson et al., 1975
		liver[b]	0.18±0.01	0.06±0.01	
		kidney[b]	0.19		
CFE rat (6) (male, 200-250 g)	2.5 in arachis oil	fat[b]	0.20±0.03	1.65±0.15	Hutson et al., 1975
		liver[b]	<0.004	0.30±0.07	
		kidneys[b]	0.19	0.04	
CFE rat (3) (male, 200-250 g)	60 in arachis oil	brain[c]	0.07-0.11	0.27-0.31	Hutson et al., 1975
Holstein cows (2) (500 kg)	0.1 mg/kg diet twice daily for 21 days	rear leg meat[d]	0.001-0.002	<0.0001	Baldwin et al., 1976
		lumbar meat[d]	0.001-0.002	<0.0001	
		liver[d]	0.008-0.011	<0.0001	
		kidney[d]	0.0005-0.0008	<0.0001	
		renal fat[d]	0.021-0.110	<0.001-0.002	
		omental fat[d]	0.050-0.060	0.003	
		subcutaneous fat[d]	0.041-0.070	0.001-0.009	
Rattus Norvegicus (2) (male, 38a, 533 g)	50 in dimethylsulfoxide	brain[e]	0.28 (533 g)	0.11-0.14	Stickel et al., 1979a
Mus musculus mouse (6)	dose not given	brain[e]	0.07-1.00	0.04-0.08	Stickel et al., 1979a
		carcass[e]	0.88-2.00	0.07-0.10	

TABLE III-6 (cont.)

Animal (Number)	Dose (mg endrin/kg bw)	Tissue	Concentration (mg compound/kg tissue)		Reference
			Endrin	12-Ketoendrin	
Golden Syrian hamster (21)^{h} (female)	1.5 day via corn oil over 11 days	liver^{f}	1.45	p	Chernoff et al., 1979
		fetal tissue^{f} (10)^{i}	0.021±0.004	p	
	2.5 day via corn oil over 11 days	liver^{f}	2.55	p	
		fetal tissue^{f} (7)^{i}	75±36	p	
CD rat (27)^{h} (female, 175-200 g)	0.15 day	liver^{g}	0.052-0.074		Kavlock et al., 1981
		fetal tissue^{g}	<0.005	np	
(29)^{h}	0.30 day	liver^{g}	0.039-0.096		
		fetal tissue^{g}	<0.005	np	
(12)^{h}	0.45 day (all doses via corn oil over 13 days)	liver^{g}	0.261-0.323	p	
		fetal tissue^{g} (6)^{i}	0.013-0.042	p	

[a] At day 120

[b] At day 3

[c] At 7-22 hours

[d] At day 21

[e] At death

[f] At day 15

[g] At day 21 of gestation

[h] Number of litters

[i] Number of fetuses

p = present but not quantified; np = not present

TABLE III-7

Distribution of Radioactivity in Various Experimental Animals After an Acute Oral Dose of Endrin

Animal Species	Admin. Route	Sex	Dose (mg/kg)	Carrier	Animal Weights (g)	Time of Analysis	Percentage of Radioactivity Administered Found in Remaining								Reference
							Urine	Feces	Liver	Kidney	Fat	Skin	Carcass	Total	
Adult rat (CFE strain)	oral	M	2.5	arachis oil (1 mℓ)	200-250 (6)	at day 3	2.65	66	1.2	0.60	1.7	2.3	12.2	86.9	Hutson et al., 1975
		F	2.5	arachis oil (1 mℓ)	200-250 (6)	at day 3	7.50	37	2.0	0.35	8.0	4.0	28.1	87.2	
Adult mice (CF No. 1)	i.v.	M	5.0	dimethyl-sulfoxide	not given (5)	at 10 minutes	NA	NA	52[a]	NA	21[a]	NA	23[a,b] 5.2[a,c]	NA	Walsh and Fink, 1972
Adult rabbit (Dutch strain)	oral	M	2.12	olive oil (10 mℓ)	2.2 kg (1)	at day 13	37.3	49.2	NA	NA	NA		13.5	100	Bedford et al., 1975b
Cow (Holstein)	oral	F	0.1 mg/kg diet (twice daily for 21 days)	corn oil; adminis-tered as capsule	450-650 kg	at day 21	55-57	19-21	0.6-1.5 in major organs		8.0	NA	3.7-5.3	88-91	Baldwin et al., 1976

[a] mg/kg tissue basis

[b] Brain level

[c] Blood level

NA - Not analyzed; M - male; F - female; i.v. - intravenous

Hutson et al. (1975) showed that endrin administered in the diet to 6 male and 6 female rats (200-250 g) was quickly metabolized and then eliminated as conjugates. The amount of conjugate was shown to be gender-dependent, confirming the earlier work of Korte (1967), Korte et al. (1970) and Baldwin et al. (1970). Three days after an acute oral dose of 2.5 mg endrin/kg bw in arachis oil by oral gavage, the fat, liver and kidneys of male rats contained the levels shown in Table III-6 and 31% of the administered dose was still retained by the animals. For females the corresponding levels are again provided in Table III-6; 56% of the administered dose was still retained. Female rats accumulated more endrin than male rats, but mostly in fat and skin. When 3 male rats were administered 60 mg endrin/kg bw by gavage, the brains of the dead animals (after 7-22 hours) contained 0.02-0.11 mg endrin/kg tissue and levels of 0.25-0.31 mg 12-ketoendrin/kg tissue. The brain levels of delta-ketoendrin, 3-hydroxyendrin, syn-12-hydroxyendrin and anti-12-hydroxyendrin were <5 µg/kg tissue. Distribution of radio-labeled ^{14}C-endrin in the experiments for both genders is provided in Table III-7.

Baldwin et al. (1976) dosed two Holstein cows (500 kg) with 0.1 mg ^{14}C-endrin/kg diet twice daily for 21 days. At day 21, the tissue levels of endrin and 12-ketoendrin in Table III-6 were found. Endrin constituted the vast majority of the residues in rear leg and lumbar meat, the liver, kidney and in renal, omental and subcutaneous fat. 12-Ketoendrin was detected in the fat but not the lean meat. Some anti-12-hydroxyendrin was detected (0.020 mg/kg ww) in the subcutaneous fat of one cow. Otherwise, the amounts of anti- and syn-12-hydroxyendrins and 3-hydroxyendrin were below detection limits. The distribution of radio-labeled endrin is provided in Table III-7 for the residues 3 weeks after administration. Minor residues remained in the major organs. All of the tissue residues were essentially endrin itself (see Table III-6).

Stickel et al. (1979a), using two old, large rats (*Rattus norvegicus*; 381 g and 533 g), administered a dose of 50 mg endrin/kg bw in a DMSO carrier. 12-Ketoendrin was detected in the brains and carcass of both rats and endrin was also found in the carcass of the fatter animal (see Table III-6). One male (542 g) and one female (331 g) rat were also fed a diet containing 150 mg endrin/kg diet until death (16 days for the male; 24 days for the female). No endrin was detected in the brain or carcass of either animal. The levels of 12-ketoendrin in the brain and carcass were 0.18 and 0.28 m/kg tissue for the male; and 0.13 and 0.13 for the female, respectively. The number of animals in the rat experiments is too small for statistical purposes but the results do agree in general with those of Hutson et al. (1975). Stickel et al. (1979a) also found that the residues of endrin in the brains and carcasses of 6 white mice killed by eating endrin-treated pine seed, and pooled in groups of three, varied from 0.70-1.00, and 0.88-2 mg endrin/kg tissue, respectively. The corresponding figures for 12-ketoendrin were 0.04-0.08 and 0.07-0.10 mg/kg tissue.

Bedford et al. (1975b), in experiments on male adult rabbits (Dutch strain; 2.2 kg) involving an acute oral dose of 2.12 mg endrin/kg bw, found low levels of endrin in the liver and in the carcass at day 13 (13% retention) (see Table III-7). At day 49, only 3.2% remained in the body.

Endrin and 12-ketoendrin were detected and confirmed by GC/MS in the liver and fetal tissue of the hamster (Chernoff et al., 1979). Timed pregnant Golden Syrian hamsters (LVG strain) were housed two per cage at 22-24°C under controlled lighting (16-hour light) after successful copulation. The animals were fed commercial lab chow and water ad lib. The endrin was administered at day 4 or at day 8 after copulation by gastric intubation in a corn oil vehicle. Single dose exeriments on nonpregnant and pregnant animals were at 0, 0.5, 1.5, 5.0, 7.5 and 10 mg/kg bw (the number of pregnant animals were 76, 10, 34, 50, 34 and 24, respectively). In multiple dose experiments, the doses were 0, 0.75, 1.5, 2.5 and 3.4 mg/kg/day (the number of surviving animals were 50, 19, 21, 12 and 2, respectively). At sacrifice (day 15) the 2.5 and 1.5 mg/kg/day dose groups yielded the endrin levels given in Table III-6. These results indicated that endrin crosses the placental barrier in hamsters. Although the authors stated that 12-ketoendrin crossed the placental barrier, it is uncertain whether 12-ketoendrin was formed from endrin in the fetus or penetrated the placental barrier from the mother.

A similar type of study on rats was also performed by the same group (Kavlock et al., 1981). Again 12-ketoendrin and endrin was found in maternal liver and in the fetus. Pregnant CD rats (175-200 g) were exposed, as in the Chernoff et al. (1979) study, to endrin doses of 0.450, 0.300, 0.150, 0.075 and 0 mg/kg/day on days 7-20 of gestation, and killed on day 21 of gestation. The number of pregnant animals studied for the respective doses were 12, 29, 27, 14 and 29. The results for the three highest doses are contained in Table III-6. Although 12-ketoendrin was identified, it was not quantitated. The average ratio of peak height of 12-ketoendrin to that of endrin was 0.19 (range 0.07-0.47) for maternal livers and 0.35 (range 0.07-0.71) for the fetus. In the hamster fetus the ratio was 3.2±0.6 (10 fetuses) at a maternal dose of 1.5 mg/kg/day. Thus in the rat, passage of endrin through the placenta will occur above a critical concentration threshold in the blood produced by an oral dose between 0.300 and 0.450 mg/kg/day.

Mechanisms of Transport and Metabolism

The metabolic pathway for endrin in mammals is complex (Figure III-1) and varies from species to species. In all species the unsubstituted methylene bridge (C_{12}) in endrin (compound I in Figure III-1) is preferentially attacked to form mostly *anti*- and lesser amounts of *syn*-12-hydroxyendrin, the latter being quickly oxidized by microsomal mono-oxygenases to produce 12-ketoendrin (compound IV in Figure III-1). To a smaller extent hydroxylation at the 3-positon also probably occurs, and the epoxide functional group is probably hydrated. *Syn*- and *anti*-12-hydroxyendrin are most likely interconvertible *in vivo* probably by 12-ketoendrin. Hydroxylation at C-3 and C-4 is inhibited by the presence of the bulky hexachlorinated fragment (Hutson, 1981). Studies in rats (Cole et al., 1970) have indicated that ^{14}C-radiolabeled-endrin is quickly metabolized to the *anti*-12-hydroxyendrin (compound II in Figure III-1), which is excreted in the bile (70% within 24 hours) as the glucuronide (Hutson et al., 1975). After enterobacterial deconjugation and enterohepatic circulation, elimination occurs as the aglycone (~45%) in the feces together with two other minor metabolites, 3-hydroxyendrin (compound V in Figure III-1) and 4,5-*trans*-dihydroisodrindiol (compound VI in Figure III-1). The major urinary metabolite in male rats (only 1-2% of the administered dose) is 12-ketoendrin

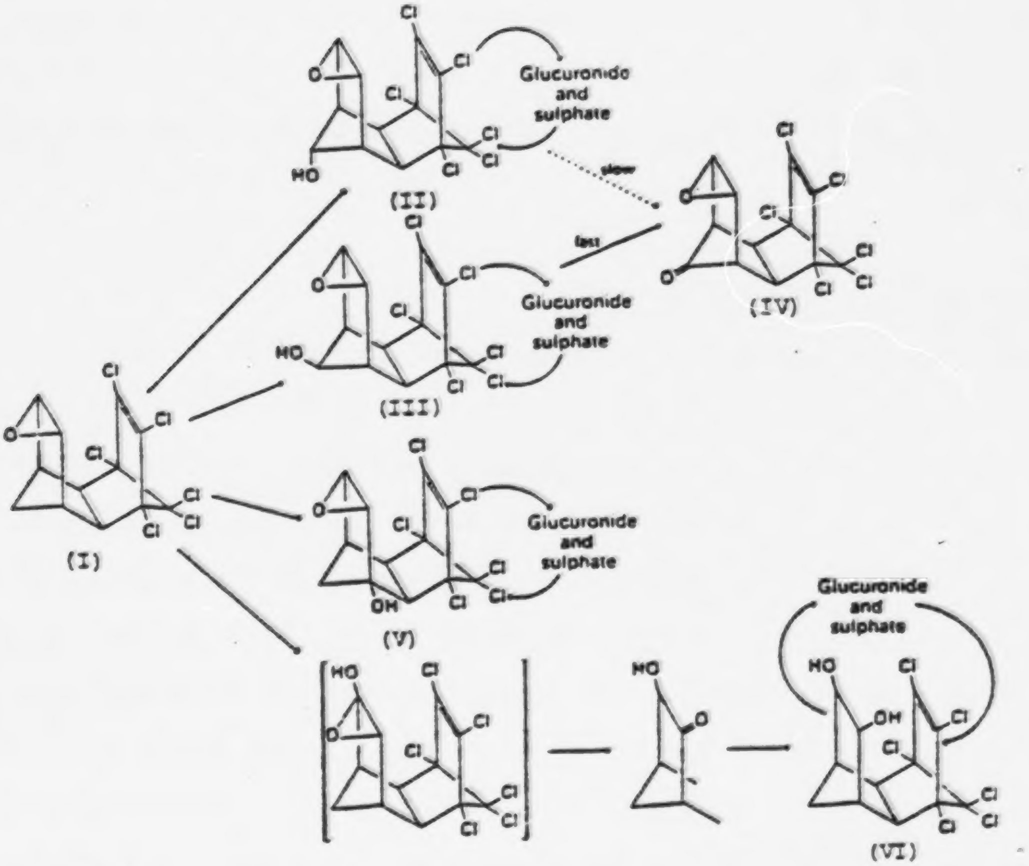

(I)
(II)
(III)
(IV)
(V)
(VI)
Glucuronide and sulphate
slow
fast
HO
OH
O
Cl

FIGURE III-1

Biotransformation of Endrin in Mammals

Source: Hutson, 1981

(compound IV in Figure III-1). This metabolite is produced by the action of microsomal mono-oxygenases on syn-12-hydroxyendrin (compound III in Figure III-1) (Hutson and Hoadley, 1974), which, in turn, is formed by attack at the unsubstituted methylene functional group of endrin. The primary hydroxylation rates in the liver for the rat and rabbit are 50:7:1.5:1 and 40:5:4:1, respectively, for anti-C-12, C-3, syn-C-12 and C-4 in that order (Bedford and Hutson, 1976). In the rabbit the major metabolite is still anti-12-hydroxyendrin, but it is conjugated with sulfate and eliminated in the urine (Bedford et al., 1975b). Some syn-12-hydroxyendrin sulfate was also found in the urine as were the glucuronide conjugates of the anti- and syn-12-hydroxyendrin, 3-hydroxyendrin, and the 4,5-trans-diol (compound VI in Figure III-1). The reason for this variability is related to the molecular weight thresholds for biliary excretion of anions in the rat and rabbit; e.g., 325±50 and 475±50, respectively (Hirom et al., 1972). The threshold for man is between these values but is closer to that of the rabbit.

The rapid metabolism has been explained in terms of the steric influence of the epoxide anion on C-12-hydroxylation in promoting anti-C-12-hydroxylation. The bulky hexachlorinated fragment inhibits attack at C-3 and C-4.

Anti-12-hydroxyendrin has been detected in the feces of factory workers (Baldwin and Hutson, 1980), and its β-glucuronide has been detected in the urine (Baldwin and Hutson, 1980). The levels of the latter appear to be dose-dependent. The toxic metabolite 12-ketoendrin was not detected in the urine and feces, neither was 3-hydroxyendrin (compound V in Figure III-1) or the diol (compound VI in Figure III-1).

These transformations are of interest because syn- and anti-12-hydroxyendrin and 12-ketoendrin all have lower LD_{50} values than endrin itself. As these metabolites are produced quickly they could be responsible for the toxic effects elicited by endrin administration. 12-Ketoendrin has been suggested as the acute toxicant (Bedford et al., 1975a).

Elimination

Endrin is rapidly eliminated both in animals and in humans. The urine is the major excretory route in cows and rabbits but is of minor importance in the rat. Endrin is both metabolized and excreted unchanged in proportions that vary with species and gender.

When ^{14}C-labeled endrin was given orally and by i.v. to rats, the keto metabolite of endrin and other hydrophilic metabolites were present in trace amounts in the urine (Klein et al., 1968). After a single i.v. dose of ^{14}C-endrin, 90% of the label was eliminated in the bile by the second day (Cole et al., 1970).

Baldwin et al. (1970) found that endrin was metabolized in the rat to at least three metabolites. One metabolite, 12-ketoendrin, was found in the urine. The other two metabolites were excreted in the feces and were not found in body tissues (Baldwin et al., 1970). The second metabolite was an isomer of 12-hydroxyendrin. This isomer had the hydroxyl group anti with respect to the epoxy group. According to Korte et al. (1970), 12-hydroxyendrin accounted for 95% of the radioactivity excreted by rats. The third metabolite was a monohydroxylated endrin, but it was not substituted at carbon 12 (Baldwin et al., 1970). The unsubstituted methylene bridge was thus hydroxylated, and the corresponding ketone was found in adipose tissue, liver and brain.

Rabbits excreted radioactivity after i.v. administration of ^{14}C-labeled endrin mainly in the urine and only as metabolites (Korte et al., 1970). Four metabolites were found in order of decreasing polarity in the ratio of 1:1:3:1. The second most polar one was identical to the 12-hydroxyendrin, which was the main metabolite found in rats. The biological half-life of endrin in male rats receiving 0.4 mg/kg diet was 2-3 days; in females, ~4 days (Korte et al., 1970). Following i.v. injection of 200 µg of ^{14}C-labeled endrin/kg/bw in two doses, male rats retained 5.2% and females 12.1% of the radioactivity after 24 hours. The radioactivity was totally excreted as metabolites (Korte et al., 1970), When ^{14}Clabeled endrin was fed to male and female rats, the males excreted 60% of it in the feces within the first 24 hours, and the females only 39%; <1% was excreted in the urine. Of the total radioactivity excreted in the feces, 70-75% occurred in the form of hydrophilic metabolites. Twenty-four hours after the last dose only metabolites were excreted (Korte et al., 1970).

The elimination and distribution of ^{14}C-labeled endrin administered acutely to rats (Hutson et al., 1975), mice (Walsh and Fink, 1972), rabbits (Bedford et al., 1975b) and cows (Baldwin et al., 1976) are provided in Table III-7.

Hutson et al. (1975) showed that 55-57% of ^{14}C-endrin was eliminated, mostly as the glucuronide of anti-12-hydroxyendrin, in the bile within 24 hours of administration to rats of 0.76-1.53 mg ^{14}C-endrin/kg bw. Other minor components (<10%) were the glucuronides of 3-hydroxy- and 12-ketoendrin. Male rats eliminated 69% of the label within 3 days whereas female rats eliminated 45%. Feces from male and female rats fed for 2 weeks on endrin diets contained the following: endrin (11%), *anti*-12-hydroxyendrin (83%), *syn*-12-hydroxyendrin (<0.01%), 3-hydroxyendrin (5%), 12-ketoendrin (1%) and delta-ketoendrin (<0.01%). Day 1 urine samples contained 17:2:0:1:10:0 proportions for males, while those from females contained 1-2% endrin but no 12-ketoendrin, the major component being 12-hydroxyendrin-O-sulfate.

Only traces of 12-ketoendrin were found in male rabbit urine after 6 days of elimination and none in rabbit feces (Bedford, et al., 1975b), even though 50% of ^{14}C-label was excreted in the urine. Nearly all (>99.5%) of the ^{14}C-label in feces within 24 hours was endrin itself, and endrin metabolites were excreted slowly over several days. Excretion of the label was 87% completed within 13 days. In urine up to 24 hours, the following compounds were found: 12-ketoendrin (7%), the glucuronide of *anti*-12-hydroxyendrin (21%), *anti*-12-hydroxyendrin sulfate (53%), *syn*-12-hydroxyendrin sulfate and 3-hydroxyendrin sulfate (14%); the glucuronide of *trans*-4,5-dihydro-isodrin-4,5-diol glucuronide (2%), and other minor glucuronides (3%). These components accounted for 40% of the single oral intake of ^{14}C-endrin. While the bulk of endrin metabolites are excreted directly by the rat in the bile (Hutson et al., 1975), mostly as glucuronides, the rabbit excretes them directly as sulfates in the urine (Bedford et al., 1975b). This behavior is consistent with molecular weight thresholds for biliary excretion, which are 325±50 in the rat and 475±50 in the rabbit (Hirom et al., 1972).

The molecular weight threshold for biliary excretion in man lies between those of the rat and the rabbit but is closer to that of the rabbit. While metabolism of endrin in humans has not been studied systematically, anti-12-hydroxyendrin as the glucuronide has been found in both feces and urine of endrin workers (Baldwin and Hutson, 1980) (Table III-8). 12-Ketoendrin was not detected (Hutson, 1981). Thus, available information suggests that endrin is probably metabolized similarly in humans and in rats and rabbits, though the proportion and the type of conjugation products differ. Baldwin et al. (1976) showed that the sulfate conjugate of anti-12-hydroxyendrin was the major metabolite in hens. Endrin was the only other excretion product in feces, generally at levels 25-35% less than the sulfate conjugate of anti-12-hydroxyendrin which generally was at levels of 4-20 mg of endrin equivalents/kg (Baldwin et al., 1976). Cows probably excrete the glucuronide in the bile, but after enterohepatic circulation the free metabolite is excreted in the urine and feces (see Table III-7). 12-Ketoendrin is also excreted in the urine of cows to the extent of 2-26% of the total administered ^{14}C-endrin (Baldwin et al., 1976) During daily treatment a steady-state of ^{14}C-label in the urine of cows is attained at about day 9.

A brief half-life of the order of a day for humans is consistent with the lack of persistence of endrin in human tissues (Coble et al., 1967), and with the rapidity with which plateau concentrations are reached in other mammals on chronic exposure, i.e., <1 week for blood endrin (Richardson et al., 1967). This observation suggests that the biological half-life of endrin in the dog is also of the order of 1-2 days.

TABLE III-8

Analysis of Urine from Endrin Plant Workers in England[a]

Worker	Concentration of Total anti-12-hydroxyendrin[b] (μg/mℓ)	12-Ketoendrin[c] (μg/mℓ)	anti-12-Acetoxyendrin after Acetylation, Expressed as Alcohol (μg/mℓ)
1	0.010	NR	NR
2	0.14	0.13	0.13
3	0.098	NR	NR
4	0.040	NR	0.037
5	0.021	NR	0.024
6	0.098	0.075	NR
7	0.011	0.015	NR

[a] Source: Baldwin and Hutson, 1980

[b] Measured after β-glucuronidase cleavage

[c] Produced after oxidation. Expressed as alcohol.

NR = Not reported

Two cows given 0.1 mg ^{14}C-endrin/kg diet twice daily for 21 days excreted the label in the milk and a steady-state was attained in 4-6 days, mostly as free endrin. The anti- and syn-12-hydroxyendrin, 3-hydroxyendrin and 12-ketoendrin were below detection limits (Baldwin et al., 1976). The estimated half-life is 2-3 days.

In August, 1976, a Canadian dairy herd was treated with endrin for control of flies; 25 animals developed poisoning symptoms, and one cow and one calf died (Frank et al., 1979). The next day after the poisoning a composite milk sample contained 0.40 ppm endrin (8.7 ppm in the milkfat). After 34 days the levels were 0.0026 ppm (0.056 ppm in the milk fat). Milk from individual cows on day 13 contained endrin levels ranging from 0.031-0.16 ppm in whole milk. The residues were analyzed by EC/GC and by TLC, or by two column EC/GC.

Estimated half-lives for a variety of animal species are presented in Table III-9. These data have been estimated from the data presented in the cited references. Endrin in sheep and cattle appears to have a longer half-life than in the rest of the species.

Another interesting study involved 50 mallard drakes (960-1360 g; 1 year old) fed 20 ppm endrin for 13 days (Heinz and Johnson, 1979). Groups of five ducks each were sacrificed at 2, 4, 6, 8, 16, 32 and 64 days after the end of dosing. Endrin was monitored in the blood and carcasses. The carcass lost 50% of its endrin in 3 days; the second halflife required an additional 8.9 days, and it took 32.9 days to lose 90% of the original amount administered. On a lipid-weight basis the first halflife of elimination was 2.2 days; the second took an additional 6.7 days and

TABLE III-9

Estimated Half-Lives in Various Species for Elimination of Endrin Administered by the Oral Route*

Species	Estimated Half-Life (dose)	Reference
Rat (M or F)	2 days (16 µg/kg) 6 days (128 µg/kg)	Korte, 1967; Korte et al., 1970
Rat (M) (i.v.) (F) (i.v.)	2-3 days (200 µg/kg) 3-4 days (200 µg/kg)	Korte, 1967; Korte et al., 1970
Rat (M) (F)	2-3 days (2.5 mg/kg) 4 days (2.5 mg/kg)	Hutson et al., 1975
Rabbit (M)	≤1 day (2.12 mg/kg) 13 days in feces alone (2.12 mg/kg) 49 days in urine alone (2.12 mg/kg)	Bedford et al., 1975b
Dog (M)	1-2 days (0.1 mg/kg/day)	Richardson et al., 1967
Man	1-2 days in blood serum	Coble et al., 1967
Sheep	1.8-8.2 weeks	Robinson, 1962
Cattle	1.8-8.2 weeks	Robinson, 1962
Mallard duck	3 days (subchronic feeding)	Heinz and Johnson, 1979
Hen	1 month from fat (chronic feeding)	Cummings et al., 1966
Cow	2-3 days	Baldwin et al., 1976

*These half-lives are based on the initial quick excretion. Acute administration was performed unless otherwise indicated.

M = male; F = female

a 90% loss of the administered amount took 24.8 days. For blood the first and second half-times and the 90% loss time on a ww basis were 1.7, 5.2 and 19.1 days, whereas on a lipid basis, these values were 1.4, 4.3 and 15.9 days, respectively.

Cummings et al. (1966) fed laying White Leghorn hens a combination of endrin, lindane, dieldrin, DDT and heptachlor epoxide at levels of 0.05, 0.15 or 0.45 ppm of each compound in the feed. After 14 weeks the birds were returned to the basal diet for 32 days. Hens in the 0.45 ppm group accumulated ~3.4 ppm endrin in the fat and required about a month to reduce the level to 50%. This increase in half-life may reflect the presence of the other pesticides. However, Baldwin et al. (1976) showed that hen eggs concentrated ^{14}C-endrin during a dosing program of 0.13 mg endrin/kg diet over a period of 148 days to the extent of 0.11-0.18 mg endrin equivalent/kg yolk. The label was identified entirely as free endrin. Thus, accumulation in eggs is a major pathway of elimination for hens.

Summary

The major route of absorption for humans appears to be through food. The average dietary intake in 1973 was 0.5 ng/kg bw/day. Special groups at risk appear to be occupational workers in the pesticide manufacturing and formulating industries. Industrial and field workers may be exposed by both dermal and respiratory routes. Several episodes of accidental and suicidal endrin poisoning in humans have occurred. Poisoning has been caused by endrin doses as low as 0.2 mg/kg. Endrin levels in drinking water are usually <100 ng/ℓ. Endrin intoxication may occur in humans at blood levels of 50-100 ng endrin/mℓ blood. These data indicate endrin can be absorbed in humans. Quantitative absorption rate data are not available for mammals.

Fat appears to be the major storage tissue for endrin in lambs and birds. The weighted average BCF in the edible portion of all freshwater and estuarine aquatic organisms is 3970.

The unsubstituted methylene group of endrin is preferentially and quickly attacked to form mostly *anti*- and lesser amounts of *syn*-12-hydroxyendrin. The latter is rapidly oxidized by microsomal mono-oxygenases to produce 12-ketoendrin. Hydroxylation at the 3 position and epoxide hydration may occur to a small extent. *Syn*- and *anti*-12-hydroxyendrin are likely to be interconvertible *in vivo* probably by 12-ketoendrin.

Endrin residues have been found in such organs as the liver, brain and kidneys and in the fat of birds, dogs, cows, rats, mice and hamsters. No 12-ketoendrin has been found in tissues of birds. Endrin appears to penetrate the blood-brain barrier in rats and hens but less readily in the cow and the placental barrier in rats, mice and hamsters, although much less efficiently for rats. 12-Ketoendrin may also penetrate the placental barrier of these three species.

In rats over 50% of the endrin metabolites are eliminated in the bile within 1 day as glucuronides which, after enterobacterial degradation and entherohepatic circulation, are eliminated as aglycones in the feces.

12-Ketoendrin is the major urinary metabolite. Females excrete endrin metabolites more slowly than males. Cows excrete free 12-hydroxyendrin after enterohepatic circulation. 12-Ketoendrin is the only other major metabolite in cow urine.

Though the major metabolite is still anti-12-hydroxyendrin in male rabbits, it is conjugated as the sulfate and excreted directly in the urine. This also occurs in hens.

The anti-2-hydroxyendrin has been detected as its glucuronide in the urine and feces of humans.

Hens appear to eliminate endrin faster than most other birds. The sulfate conjugate of anti-12-hydroxyendrin is the major metabolite in hen feces. The only other metabolite is endrin itself. Endrin does appear to accumulate more in birds than in mammals.

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as endrin from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to endrin is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Detailed information concerning the occurrence of and exposure to endrin in the environment is presented in another document entitled "Occurrence of Pesticides in Drinking Water, Food, and Air" (Johnston et al., 1984). This chapter summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

In the Exposure Estimation section of this chapter, available information is presented on the range of human exposure and intake for endrin from drinking water, food and ambient air for the 70-kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources. However, the Summary section of this chapter provides some insight into the relative contributions of the three sources, especially drinking water, to the range of intake values suggested by the available data.

Exposure Estimation

Drinking Water. Levels of endrin in drinking water vary from one location to another. The highest level of endrin monitored in the available studies was 0.008 μg/ℓ in New Orleans (U.S. EPA, 1975, as cited in Pellizzari, 1978), well below the Maximum Contaminant Level (MCL) of 0.2 μg/ℓ. Analysis of the National Screening Program for Organics in Drinking Water (NSP) (Boland, 1981) suggests that median levels of endrin in drinking water would be below 0.1 μg/ℓ, since none of 116 systems sampled contained a level of endrin above 0.1 μg/ℓ. In addition, analysis of the Rural Water Survey (RWS) (U.S. EPA, 1984) suggests that median levels of endrin in drinking water systems would be <0.008 μg/ℓ, since none of 92 systems sampled contained a level of endrin >0.008 μg/ℓ. Endrin may not be present in drinking water in some areas. The available monitoring data are not sufficient to determine regional variations in levels of exposure to endrin.

The daily intake of endrin from drinking water was estimated using the assumptions presented in Table IV-1 and the values presented above. The estimates in Table IV-1 indicate that the daily intake of endrin from drinking water ranges from 0.0-0.0028 μg/kg/day. However, the values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

TABLE IV-I

Estimated Daily Intake of Endrin from Drinking Water*

Drinking water concentration (μg/ℓ)	Intake (μg/kg/day)
0.0	0.0
0.008	0.0002
0.1	0.0028

*Assumptions: 70-kg man consuming 2 ℓ of water/day.

Diet. Data are limited on the dietary intake of endrin in the United States. For fiscal year 1979, the only positive value for endrin in an FDA market basket study on toddlers (FDA, 1982a,b). In this study, an estimated dietary intake of 0.0001 μg/kg/day was calculated based on endrin levels in an oil and fat composite (FDA, 1982b).

Additional data were obtained on the estimated total dietary intake of endrin for adults in the years 1974-1979 and for infants and toddlers in the years 1975-1979 (Table IV-2). The average total intakes for adults, infants and toddlers over the years studied was 0.000008, 0.00004 and 0.00016 μg/kg/day, respectively.

Using the above data, the daily adult intake of endrin is estimated to be 0.000008 μg/kg/day. This value does not account for variances in individual exposure.

It is expected that dietary levels of endrin vary somewhat with geographical location, with higher levels occurring in foods from areas near the sources of endrin exposure. However, because of insufficient data, no estimates could be made of variations in intake by geographical region.

EPA has established a tolerance of zero for endrin in and on the following raw agricultural commodities: sugar beets, sugar beet tops, broccoli, Brussel sprouts, cabbage, cauliflower, cotton seed, cucumbers, eggplant, peppers, potatoes, summer squash and tomatoes (40 CFR 180.131, July 1, 1981).

TABLE IV-2

Estimated Total Daily Dietary Intake of Endrin for Adult Male, Infant, and Toddler

	Intake (μg/kg/day)		
Year	Adult male[a]	Infant[b] (6 months)	Toddler[b] (2 years)
1974	ND	--	--
1975	Trace[c]	ND	ND
1976	ND	ND[d]	0.0007
1977	0.00004[c]	ND	ND
1978	ND	0.0002	ND
1979	ND	ND	0.0001
Average[e]	0.000008	0.00004	0.00016

[a] From FDA 1981, except as noted.

[b] From FDA 1980b, 1982b.

[c] Calculated based on information in Johnson and Manske 1977 and FDA 1980a.

[d] Appears to be an error since a positive value was reported in Johnson et al. 1981.

[e] Trace values were not included in the calculation; nondetected values were assumed to be equal to zero.

ND = None detected.

Air. Levels of endrin in the atmosphere also vary from one location to another. The highest level of endrin reported was 39.3 ng/m³ (0.0393 µg/m³) in the Mississippi Delta in 1972-1974 (Arthur et al., 1976). In a national study the highest level of endrin reported was 19.2 ng/m³ (0.0192 µg/m³) in Tennessee in 1971 (Kutz et al., 1976). Typical levels, however, are somewhat lower. An estimated mean level of endrin in ambient air, based on the information in Kutz et al. (1976), is 0.2 ng/m³ (0.0002 µg/m³). (However, this estimate is based on data from 1970-1972 and obtained in sampling locations with potentially high concentrations of pesticides in ambient air.) Additionally, concentrations of endrin are below the limits of detection in some areas and may be as low as 0.0 ng/m³. The available monitoring data are not sufficient to determine regional variations in levels of exposure to endrin.

The daily respiratory intake for endrin from air was estimated using the assumptions presented in Table IV-3 and the values presented above. The estimates in Table IV-3 indicate that daily endrin intake from air ranges from 0.0-0.013 µg/kg/day. These values do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Summary

This section considers the relative contribution of drinking water, food and ambient air to the total human exposure from these three sources. The data presented here indicate the potential total exposure to endrin that could occur if a population was exposed to specific combinations of endrin concentrations in drinking water, food and ambient air.

TABLE IV-3

Estimated Daily Respiratory Intake of Endrin*

Air concentration ($\mu g/m^3$)	Intake ($\mu g/kg/day$)
0.0	0.0
0.0002	0.00007
0.0192	0.0063
0.0393	0.013

*Assumptions: 70-kg man inhaling 23 m^3 of air/day (ICRP, 1975).

Table IV-4 presents a general view of the total amount of endrin that may be received by an adult male from air, food and drinking water. Four separate exposure levels in air, three exposure levels in drinking water, and one exposure level from foods are shown in the table.

The data in Table IV-4 have been selected from an infinite number of possible combinations of concentrations for the three sources. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to endrin at any of the combined exposure levels. The data represent possible exposures based on the occurrence data and the estimated intake data.

A mean level for endrin in ambient air of 0.0002 μg/m³ was estimated. Assuming a level of 0.0002 μg/m³ in ambient air and the estimated endrin intake of 0.000008 μg/kg/day from foods, drinking water would be the predominant source of exposure to endrin for the adult male at drinking water levels >0.003 μg/ℓ.

The total estimated intake of endrin is <0.020 μg/kg/day. This value is much lower than the FAO/WHO and EPA acceptable daily intake of 0.2 μg/kg/day (FDA, 1981), but approaches a maximum safe level of 0.04 μg/kg/day calculated by EPA (U.S. EPA, 1976).

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for endrin by route of exposure. The relative dose received may vary with the intake. In addition, the effects of endrin on the body may vary by different routes of exposure.

TABLE IV-4

Estimated Daily Intake of Endrin from the Environment by Adult Males

Concentration in Drinking Water (µg/ℓ	Estimated Total Intake in µg/kg/day (% From Drinking Water) Based on a Concentratiaon in Air (µg/m³) of:			
	Low (0.0)	Intermediate (0.0002)	High (0.0192)	High (0.0393)
Low (0.0)	0.000008 (0%)	0.00008 (0%)	0.0063 (0%)	0.013 (0%)
Intermediate (0.008)	0.0002 (100%)	0.0003 (67%)	0.0065 (3.1%)	0.013 (1.5%)
High (0.1)	0.0028 (100%)	0.0029 (97%)	0.0091 (31%)	0.016 (17.5%)

Intake from each source:

Drinking water:	0.0 µg/ℓ:	0.0 µg/kg/day
	0.008 µg/ℓ:	0.0002 µg/kg/day
	0.1 µg/ℓ:	0.0028 µg/kg/day
Air:	0.0 µg/m³:	0.0 µg/kg/day
	0.0002 µg/m³:	0.00007 µg/kg/day
	0.0192 µg/m³:	0.0063 µg/kg/day
	0.0393 µg/m³:	0.013 µg/kg/day
Food:	0.000008 µg/kg/day	

References

Arthur, R.D., J.D. Cain and B.F. Barrentine. 1976. Atmospheric levels of pesticides in the Mississippi Delta. Bull. Environ. Contam. Toxicol. 15(2): 129-134.

Boland, P.A. 1981. National screening program for organics in drinking water. Part II. Data. Prepared by SRI International, Menlo Park, CA, for Office of Drinking Water, U.S. EPA, Washington, DC. EPA Contract No. 68-01-4666.

FDA (Food and Drug Administration). 1980a. Compliance program report of findings. FY 77 total diet studies -- Adult (7320.73). Food and Drug Administration, U.S. Department of Health, Education and Welfare, Washington, DC.

FDA (Food and Drug Administration). 1980b. Compliance program report of findings. FY 77 total diet studies -- Infants and toddlers (7320.74). Food and Drug Administration, U.S. Department of Health, Education and Welfare, Washington, DC.

FDA (Food and Drug Administration). 1981. The FDA surveillance index. Bureau of Foods, Food and Drug Administration, Washington, DC.

FDA (Food and Drug Administration). 1982a. Compliance program report of findings. FY 79 total diet studies -- Adult (7305.002). Food and Drug Administration, U.S. Department of Health and Human Services, Washington, DC. FDA/BF-82/98.

FDA (Food and Drug Administration). 1982b. Compliance program report of findings. FY 79 total diet studies -- Infants and toddlers (7305.002). Food and Drug Administration, U.S. Department of Health and Human Services, Washington, DC. FDA/BF-82/97.

Johnson, R.D. and D.D. Manske. 1977. Pesticide and other chemical residues in total diet samples (XI). Pestic. Monit. J. 11(3): 116-131.

Johnson, R.D., D.D. Manske, D.H. New and D.S. Podrebarac. 1981. Pesticide, heavy metal, and other chemical residues in infant and toddler. Total diet samples -- (II) -- August 1975-July 1976. Pestic. Monit. J. 15(1): 39-50.

Johnston, P., F. Letkiewicz, D. Borum, N. Gambal, G. Gerner, et al. 1984. Occurrence of pesticides in drinking water, food and air. Interim draft report. Prepared by JRB Associates, McLean, VA, for Office of Drinking Water, U.S. EPA, Washington, DC.

Kutz, F.W., A.R. Yobs and H.S.C. Yang. 1976. National pesticide monitoring programs. In: Air Pollution from Pesticides and Agriculture Processes, R.E. Lee, Ed. CRC Press, Cleveland, OH. p. 95-136.

Pellizzari, E.D. 1978. Preliminary assessment of halogenated organic compounds in man and environmental media. Monthly Technical Progress Report No. 5, April 1-April 30, 1978. Prepared by Research Triangle Institute, Research Triangle Park, NC, for Office of Toxic Substances, U.S. EPA, Washington, DC. EPA Contract No. 68-01-4731.

U.S. EPA. 1975. Analytical report: New Orleans water supply study. Region VI, U.S. EPA. EPA 906/9-75-003. (Cited in Pellizzari, 1978)

U.S. EPA. 1976. National interim primary drinking water regulations. Office of Water Supply, U.S. EPA, Washington, DC. EPA-570/9-76-003.

U.S. EPA. 1984. Rural water survey. Computer data provided by Department of Sociology, Cornell University, Ithaca, NY.

V. HEALTH EFFECTS ON ANIMALS

Acute Toxicity

Experimental Lethality Studies. Endrin is acutely toxic to a number of species when administered by oral gavage in a solvent, in the diet, or applied to the skin (Table V-1). The LD_{50} varies with the species and strain of animal used. An early comprehensive study of acute toxicity in mammals included Carworth rats (male and female of two ages), 4 rabbits, 4 guinea pigs, 1 cat and 2 monkeys (Treon and Cleveland, 1955). Minimum lethal oral doses were: monkeys, 1-3 mg/kg bw; cats and female rats, <5 mg/kg; male rats, 5-7 mg/kg; rabbits, 5-7 mg/kg; and male guinea pigs, 24-36 mg/kg. These data suggest that primates are one of the most sensitive groups. Signs of intoxication included ataxia, tremors, labored breathing, diarrhea and tonic-clonic convulsions.

Treon and Cleveland (1955) found female rats to be more sensitive to endrin than males on a mg/kg bw basis, with LD_{50}s of 16.8 mg/kg and 28.8 mg/kg, respectively, for young animals 29-31 days of age. For 6-month-old rats the LD_{50} for female rats was 7.3 mg/kg, and for male rats, 43.4 mg/kg. The same LD_{50}s were also obtained for isodrin, the industrial precursor of endrin (Treon et al., 1955). Bedford et al. (1975a), using the same strain of rat, found no difference between the response of female and male rats of 12-14 weeks of age to acute oral doses of endrin with LD_{50}s of 5.3 mg/kg and 5.6 mg/kg, respectively.

The oral LD_{50} of endrin for 6-month-old male Sprague-Dawley rats was reported to be 40 mg/kg bw by Speck and Maaske (1958). Groups of 8-12 rats were given single doses of endrin (20-80 mg/kg bw) in peanut oil by gastric

TABLE V-1

Acute Toxicity of Endrin in Experimental Animals

Animal Species	Route of Administration	Formulation	LD_{50} in mg/kg bw Male	LD_{50} in mg/kg bw Female	Reference
		MAMMALS			
Rat, young[a]	oral	peanut oil	28.8	16.8	Treon et al., 1955
Rat, adult[a]	oral	peanut oil	43.4	7.3	Treon et al., 1955
Rat, adult[a]	oral	peanut oil	40.0	NR	Speck and Maaske, 1958
Rat[a]	oral	20% e.c.[b]	6.6	3.4	Muir, 1968
Rat[a]	oral	2% f.s.d.[c]	2.5	6.6	Muir, 1968
Rat[a]	dermal	20% e.c.[b]	10.9	NR	Muir, 1968
Rat[a]	dermal	2% f.s.d.[c]	31.5	92	Muir, 1968
Rat	dermal		15-18		Gaines, 1969
Rat[a]	oral	DMSO[d]	5.6	5.3	Bedford et al., 1975a
Rat[a]	oral	arachis oil	NR	5.3	Bedford et al., 1975b
Mouse[e]	i.v.	DMSO[d]	2.3	NR	Walsh and Fink, 1972
Mouse[f]	i.p.	corn oil	5.6	NR	Graves and Bradley, 1965
Hamster	oral	corn oil	12	17.0	Cabral et al., 1979
Hamster	oral	corn oil	NR	18.6	Chernoff et al., 1979

TABLE V-1 (cont.)

Animal Species	Route of Administration	Formulation	LD_{50} in mg/kg bw		Reference
			Male	Female	
Rabbit	oral	peanut oil	7-10	NR	Treon et al., 1955
Rabbit	dermal for 24 hours	dry, 100-mesh powder	NR	130-160	Treon et al., 1955
Guinea pig	oral	peanut oil	36[g]	16[g]	Treon et al., 1955
Dog (mongrel)	i.v.	95% ethanol	2-3[g]	NR	Reins et al., 1966
Cat	oral	peanut oil	5[h]	NR	Treon et al., 1955
Monkey	oral	peanut oil	3[g]	3[g]	Treon et al., 1955
		BIRDS			
Pigeon	i.v.	NR	1.2-2.0	1.2-2.0	Revzin, 1966
Mallard	oral	corn oil	NR	5.64	Hudson et al., 1979
Mallard	percutaneous	corn oil	>140	NR	Hudson et al., 1979

[a] CFE

[b] Emulsion concentration

[c] Field strength dust

[d] Dimethylsulfoxide

[e] Carworth Farms No. 1 strain

[f] Swiss-Webster and ICR strains of Swiss albino mice

[g] Estimated

[h] Minimum lethal dosage

intubation. There was a latent period of 45-60 minutes before the onset of convulsions, regardless of the dose. Deaths occurred within 24-72 hours. Gross examination at autopsy revealed contracted spleens, congested lungs, and bright red blood, along with reddened livers and viscera. No histologic changes were apparent in sections of liver tissue. Electroencephalogram recordings after acute doses showed irregular slowing, irregular spikes, and convulsive discharges. The righting reflex was not abolished during convulsions unless the attack was terminal. Pentobarbital stopped convulsions but did not prevent death. Trypan blue (2 mℓ of 1% solution) given with 50 mg endrin/kg bw to 30 rats prevented convulsions and lowered the death rate up to 80 hours post-treatment. All animals given endrin alone were dead at 200 hours after dosing and ~7% of the trypan blue-treated rats survived. No convulsions were seen in animals with the choroid plexus stained blue by the dye. These observations suggested that the acute reaction may involve increased blood-brain barrier permeability and that the concentration of endrin had to reach a critical level in either the blood or brain tissues before convulsions occurred.

Graves and Bradley (1965) calculated an LD_{50} of 5.6 mg/kg bw for endrin in corn oil injected into the peritoneal cavity of Swiss-Webster and ICR strains of Swiss albino mice. No mortality was seen in controls (13 mice) or at dosages of 1 mg/kg (8 mice) or 2 mg/kg (8 mice). Complete mortality was obtained with dosages $\geq$10 mg/kg (8 mice). Observations of survivors during an additional 6-day period revealed no further mortality. Similar observations have been reported for humans when individuals survived the symptomatic stage (Curley et al., 1970).

Acute i.v. LD_{50} values and median survival times (ST_{50}) of male mice (10/group) exposed to endrin were determined to be 2.3 mg/kg bw (2.0-2.6, 95% confidence limits), and 17.5 minutes (15.2-20.1, 95% confidence limits at a dose of 3 mg/kg), respectively (Walsh and Fink, 1972). Endrin was administered in DMSO. At an LD_{90} (5 mg/kg), the ST_{50} was 11 minutes. In adult male mice (CF1 strain), a latent period of no activity that followed injection ended abruptly with a first clonic convulsion. Intermittent clonic seizures ended with the beginning of hind leg tonic activity. Post-tonic activity involved continual clonic seizures which terminated in some cases in death. The dose which produced ataxia in 50% of the mice was 0.75 mg/kg (0.59-0.98, 95% confidence limits). The authors suggested that the mechanism of toxicity may be due to effects on plasma membranes or mitochondrial ATPases in the brain or both.

Bedford et al. (1975a) determined the acute oral LD_{50} values (based on 10-day mortality) for three metabolites of endrin which have been identified in mammals (Baldwin et al., 1970; Bedford et al., 1975a). Each metabolite was more acutely toxic than the parent pesticide (Table V-2). _Syn_-12-hydroxyendrin and 12-ketoendrin were about 5 times more toxic than the parent compound in male rats; in females, 12-ketoendrin was 5 times and _syn_-12-hydroxyendrin 2 times more toxic than endrin. _Anti_-12-hydroxyendrin was 2 times more toxic in male rats and equitoxic to endrin in females. The most rapidly lethal compound was 12-ketoendrin; mortality was observed within 20 hours of administration for both male and female rats. Endrin and the isomers of 12-hydroxyendrin produced mortality in 4-6 days in male rats, and 5-8 days in female rats. The authors concluded that even though oxidative

TABLE V-2

Median Lethal Doses 10 Days After Oral Administration of Endrin and Its Metabolites to Rats[a]

Compound	LD_{50} (mg/kg)[b,c]	
	Male	Female
Endrin	5.6 (3.0-7.9)	5.3 (3.6-7.4)
anti-12-Hydroxyendrin	2.4 (2.0-3.0)	5.5 (4.2-7.2)
syn-12-Hydroxyendrin	1.2 (0.6-1.7)	2.8 (0.8-4.0)
12-Ketoendrin	1.1 (0.7-1.5)	0.8 (0.5-1.2)

[a] Source: Bedford et al., 1975a

[b] Administered by gavage in DMSO to CFE strain rats, 12-14 weeks of age, divided into groups of either 4 or 8 rats of each sex

[c] Numbers in parentheses are 95% confidence limits

metabolism of endrin is responsible for the observed efficient elimination from rats of subacute doses, oxidative products of endrin may also be responsible for its acute toxicity.

Bobwhite quail (14 weeks old) were fed a diet containing 10 ppm endrin (the endrin being solubilized in propylene glycol before incorporation into the diet). Mortality occurred on day 1 (1 bird), 6 (7), 9 (5) and 10 (2) in a group of 20 quail. Birds dying of endrin intoxication averaged weight losses of 32.2%. The five survivors were sacrificed on day 10. No mortality occurred among birds fed a control diet (Ludke, 1976).

LC_{50}s, defined as the dietary dosage (dw) required to kill 50% of the test animals in a specified period of time in this case, at 14 days were determined on short-tailed shrews (5/group) fed endrin mixed in the food after being dissolved in a mixture of soybean and cottonseed oils (Table V-3) (Blus, 1978). Short-tailed shrews were obtained from the Patuxent Wildlife Research Center, Laurel, Maryland. Male shrews were almost 2 times more sensitive to endrin ingestion than females; the LC_{50} was 87 and 152 ppm for males and females, respectively. The food ingested/body weight ratio for this rodent-like nonprimate was not reported; therefore, an actual exposure dosage cannot be calculated. The LD_{50} was not affected by the age of the shrews as the results with animals 30-75 or 105-150 days of age were identical. One group of females given endrin was >180 days of age (LC_{50}, 174 mg endrin/kg diet); males of this age were not available. Although the level of sensitivity for detecting endrin was listed as 0.2 mg endrin/kg ww for the 0.25 g shrew brain, no endrin was detected in the brains of several shrews that died on endrin dosage. Endrin levels reported for two pools of brains of three shrews each were 0.93 and 0.94 mg/kg ww.

TABLE V-3

Endrin Short-Term Oral Dietary LC_{50} Values

Species	Sex/Age	Duration	Number of Animals	LC_{50}[a] (ppm endrin in the diet)	Reference
Short-tailed shrew	F/180 days	14 days	5	174	Blus, 1978
	M/105-150 days	14 days	5	87	Blus, 1978
	F/105-150 days	14 days	5	152	Blus, 1978
	M/30-75 days	14 days	5	87	Blus, 1978
	F/30-75 days	14 days	5	152	Blus, 1978
Rat, Wistar	M, F/immature	5 days	50[b]	60.1 (43-83)[c]	McCann et al., 1981
Rat, Wistar	M, F/immature	5 days	50[b]	62.3 (45-85)[c]	McCann et al., 1981

---

[a] LC_{50} = Dietary dosage (dw) required to kill 50% of test animals in a specified period of time

[b] 5 male and 5 female/group/concentration; five concentrations

[c] 95% = Confidence limit

12-Ketoendrin levels in the shrew brains were below detection. Interpretation of the analytical data was complicated by the disagreement of two analytical laboratories reporting residue data and by the fact that nearly all of the endrin lost during sample preparation (see Chapter II).

Feeding experiments on bullfinches were designed to test a claim that endrin reduced damage to fruit trees by repellency (Feare et al., 1978). The normal seed diet was withdrawn from six bullfinches and replaced with pear buds treated with 1.5% or 0.35% endrin/kg bud. Normal diet was given after 24 hours and the endrin-treated buds left in the cages. At the end of this second 24-hour period, seed was removed again from the cages for 7 hours. Five of the 6 birds which were given 1.5% mg/kg bud, and 3 of 6 birds which were given 0.35% mg/kg bud, died. There was no evidence of a repellent effect. Again, since no food ingested/body weight ratio for bullfinches is available, the actual exposure doses cannot be calculated.

The acute toxicity of 13 pesticides was investigated in 6-week-old Syrian golden hamsters. For endrin, the LD_{50} was 17 mg/kg bw for females and 12 mg/kg bw for males (Cabral et al., 1979).

Hudson et al. (1979) compared the acute oral and 24-hour percutaneous LD_{50} values in mallards for 21 common pesticides including endrin. Oral administration was accomplished by inserting a gelatin capsule containing the chemical through glass tubing to the level of the crop or proventriculus. The oral LD_{50} of endrin to female mallards 43-56 weeks of age was

5.64 mg/kg bw (2.71-11.7, 95% confidence limit). The percutaneous LD_{50} to male mallards 45 weeks of age was reported as 140 mg/kg. Clinical signs of intoxication were induced at this level, which represented the highest level of solubility of endrin in corn oil that the investigators were able to attain under their experimental conditions.

McCann et al. (1981) advocated the use of the rat LC_{50} as a measure of the toxicity of pesticides to mammalian wildlife rather than a rat single-dose oral LD_{50} (see Table V-3). A 5-day rat dietary LC_{50} test was developed and evaluated by testing 17 pesticides, including endrin. The test used immature (90-120 g) Albino Norway rats (Wistar strain). Five rats of each sex were exposed to different concentrations of the pesticide dissolved in corn oil and added to the diet. A group of identical size was used as a control in each test, which consisted of a 5-day acclimation period, a 5-day exposure to treated food and a post-treatment observation period lasting for at least 9 days. The LC_{50} for endrin in the diet based on this test was 60 ppm, whereas the LC_{50} derived from the literature was 100 ppm. If a daily food ingested/body weight ratio of 0.10 is assumed, along with an initial body weight of 90-120 g, this would represent an ingested food intake of 4.5-6.0 g equivalent to an exposure dose of 3 mg endrin/kg initial body weight/day.

Environmental and Accidental Intoxication. The meadow vole (*Microtus pennsylvanicus*) is known to be sensitive to endrin as evidenced by the virtual disappearance of the rodent population after its habitat and food supply were sprayed once with endrin (Wolfe et al., 1963).

Panicum seed contaminated with endrin caused the deaths of ~320 cagebirds (finches, doves, quails) in an aviary. The feed was a mixture of panicum seed and canary seed containing 2.20 ppm endrin. The panicum seed portion contained 4.80 ppm endrin. Birds began dying 2 days after introduction of the contaminated feed, with the greatest number of mortalities occurring after 5 days of exposure. There were no deaths among the 80 canaries in the aviary while 290 of 350 finches died. Finches preferred the panicum seed while the canaries did not eat it. Birds with clinical signs of poisoning were unstable in flight, found it difficult to alight and often ended a flight hanging upside down by one leg. No gross or microscopic lesions were found in 12 necropsied birds (Main, 1978).

Wild birds such as grackles, mallards and white pelicans have also died of endrin intoxication (Peterson and Ellarson, 1978). Two bald eagles possibly died of endrin poisoning (Kaiser et al., 1980). Brains of the eagles contained 0.71 and 1.2 mg endrin/kg ww; the known lethal range begins at ~0.6 mg endrin/kg ww.

Misuse of endrin in India was responsible for the death of one bullock and symptoms of acute poisoning in three other animals (Pandey, 1978). The bullocks were treated for tick infestation with "concentrated" endrin over their entire bodies. Signs of poisoning occurred after 6 hours.

Endrin poisoning was reported in 15 of a herd of 70 Sa'anen adult female goats after they had been grazing in an uncultivated area of weeds later found to contain endrin-contaminated boxes. Signs included fits of trembling affecting the whole body, convulsions, profuse salivation and collapse with an inability to rise. In most cases signs subsided within a few minutes but resumed within an hour or so. Treatment with atropine, propionyl promazine, fluid (saline and Ringers), corticosteroid (prednisone) and carbachol was not effective. Within 16 hours, 8/15 goats died, with 2 more dying in the next 24 hours. Post-mortem examination revealed profuse blood-stained froth in the trachea, diffuse hemorrhagic enteritis, some petechiae on the epicardium, adhesions between the parietal and pulmonary pleurae and Cystericerus tenuicollis cysts in the abdomen, with fluid and pale intestinal contents. Quantities of endrin consistent with those found in poisoning cases were found in the content of the rumen. High residues of endrin were found in a sample cardboard box similar to one eaten by the goats in the grazing area. This incident illustrated the danger of improper disposal of containers used for storage of toxic pesticides (Rapaport et al., 1979).

When endrin was applied as a 20% emulsion, acute dermal LD_{50} values for rats were about twice the size of acute oral LD_{50} values (Muir, 1968). When endrin was applied as a field strength dust, the acute dermal LD_{50} value was more than an order of magnitude greater. However, both of these endrin preparations were more toxic than endrin administered in peanut oil, showing that LD_{50} values are vehicle dependent. Dermal administration of endrin as a dry 100-mesh powder in contact for 24 hours under a rubber sleeve with the intact skin of female rabbits yielded an acute LD_{50} between 130 and 160 mg endrin/kg bw and a minimum lethal dose between 66 and 94 mg/kg bw (Treon and Cleveland, 1955). Table V-1 summarizes these toxicity data.

Cardiovascular Effects. In the early 1960s, little was known of cardiovascular changes following acute exposure to lethal amounts of endrin. Experiments with male and female dogs to investigate these phenomena were conducted on 30 dogs weighing from 10-19 kg (Emerson et al., 1964) Anesthesia was induced with sodium pentobarbital (30 mg/kg) and, in some cases, succinylcholine was given to prevent convulsions. Endrin (10 mg/kg bw in 95% ethanol) was administered by i.v. infusion. Control animals received an equivalent amount of ethanol. Convulsions started within 5-10 minutes after the beginning of endrin infusion in dogs not given succinylcholine. Observations included bradycardia, an initial drop in arterial blood pressure, increased body temperature, hemoconcentration, decreased venous blood pH, and increased leukocyte concentration. Hemolysis was seen in every post-endrin hematocrit. Cerebral venous pressure and cerebrospinal fluid pressure elevations were also prominent features of endrin poisoning. When succinylcholine was given, the results were similar except that arterial pressure increased initially but later fell to hypotensive levels. Blood pH also decreased more and hemoconcentration was more pronounced. In controls, succinylcholine-induced bradycardia was replaced by tachycardia in some animals. The heart rate would then oscillate between bradycardia and tachycardia. These authors concluded that most of the observed effects appeared to be caused by endrin acting directly on the central nervous system, although some might have resulted secondarily from altered cerebral hemodynamics.

Endrin-induced convulsions terminating in death are accompanied by marked changed in blood pressure and heart rate. Using 50 mongrel dogs, Reins et al. (1966) determined the relationship between venous return (cardiac output), total peripheral vascular resistance and hypertension after a lethal dose of endrin. All animals were treated with succinylcholine to prevent convulsions. Endrin (10 mg/kg bw in ethyl alcohol) induced a rise in systemic arterial blood pressure which depended primarily on increased cardiac output caused by an elevated venous return. Increased levels of epinephrine and norepinephrine in blood plasma, rather than CNS stimulation, may be the explanation for the marked alterations in systemic hemodynamics. Total peripheral resistance did not change significantly in either endrin-infused dogs or control animals infused with the solvent, ethyl alcohol. In a similar study with dogs, Hinshaw et al. (1966) also reported large increases in blood catecholamine concentrations, and increased cardiac output. In contrast to the Reins et al. (1966) findings, these investigators reported that total peripheral resistance fell significantly and that cardiovascular alterations were not significantly correlated with blood catecholamines after endrin intoxication. One major difference between the two studies was that Reins et al. (1966) used succinylcholine to prevent convulsions; anesthesia was achieved with sodium pentobarbital (30 mg/kg bw) in both studies.

Tissue Concentration as Indicator of Lethal Dose. As the sensitivity and specificity of analytical methods increased, investigators of endrin toxicity analyzed brain tissue for endrin and endrin metabolites. Efforts were made to relate the concentration of residues in the brain to lethal doses of endrin. In a pharmacokinetic study of endrin in rats, Bedford et al. (1975a) measured levels of endrin and its metabolites following lethal doses of endrin. Three male rats (CFE strain) died in 7-22 hours following a lethal oral dose of 60 mg (in DMSO)/kg bw. The concentration of endrin in the brain was 0.11, 0.07 and 0.02 mg/kg ww; the concentration of 12-ketoendrin was 0.29, 0.31 and 0.25 mg/kg ww. Three males rats given an oral dose of 12-ketoendrin (16 mg/kg) died in 20-30 minutes; the brain endrin concentration was 0.005 but the 12-ketoendrin concentration was 1.36, 1.25 and 1.71 mg/kg brain tissue. Table V-4 lists some tissue concentrations as indicators of a lethal dose of endrin. Hutson et al. (1975) stated that the 12-ketoendrin metabolite of endrin found in rats "could be very significant for use in monitoring suspected acute exposure to endrin." However, little was detected in cows (except in the urine) and rabbits and none in birds (Chapter III) so that 12-ketoendrin levels in the brain are definitely diagnostic for lethality only for the rat. In a similar study, rats were given 50 mg/kg bw of endrin by intubation or 150 ppm in the diet (Stickel et al., 1979a). Residues of 12-ketoendrin in brain tissue ranged from 0.11-0.18 mg/kg ww. 12-Ketoendrin was found in the brain tissue of white mice at levels of 0.04-0.08 mg endrin/kg ww.

Stickel et al. (1979a) found no 12-ketoendrin in four orders of birds that had been heavily exposed to or killed by endrin. In a comparative study, Stickel et al. (1979a) examined frozen tissues from an endrin-exposed pelican and 12 white mice, male and female sparrow hawks, an adult male broad-winged hawk, 8 male grackles, 2 female mallards, 4 quail and a white pelican fed endrin in the diet. No 12-ketoendrin was found in the brains of male grackles, female mallards, a white pelican, quail, kestrels, or a broad-winged hawk. Of two hawks killed by eating endrin-poisoned mice, the brain of one contained 0.06 mg 12-ketoendrin/kg ww and 0.42 mg endrin/kg ww.

TABLE V-4

Tissue Concentrations in Brain as Indicators of Lethal Doses of Endrin in Selected Species of Warm-Blooded Animals

Species	Number	Indicator of Lethal Dose[a] (mg endrin/kg)	Reference
Rat	13	0.3 (12-ketoendrin)	Hutson et al., 1975
Rat (M/F)	2	0.11-0.18 (12-ketoendrin)[b]	Stickel et al., 1979a
White mouse	6	0.04-0.08 (12-ketoendrin) 0.7-1.0 (endrin)	Stickel et al., 1979a
Bobwhite quail	15	0.34-1.84 (endrin)	Ludke, 1976
Grackle	8	1.1-2.2 (endrin)	Stickel et al., 1979a
Mallard	2	0.62-1.37 (endrin)	Stickel et al., 1979a
Pelican	1	0.74 (endrin)[c]	Stickel et al., 1979a
Bald eagle	14	0.12-1.2 (endrin)[c]	Kaiser et al., 1980
Starling (M) (F)	7 7	0.85-1.24 (endrin) 1.03-1.49 (endrin)	Stickel et al., 1979b
Cowbird (M)	12	0.69-1.81 (endrin)	Stickel et al., 1979b
Redwing (F)	12	0.72-1.66 (endrin)	Stickel et al., 1979b
Grackle (M) (F)	12 10	0.88-1.67 (endrin) 0.79-1.35 (endrin)	Stickel et al., 1979b
Eagle (M/F)	2	0.92-1.2 (endrin)	Stickel et al., 1979b

[a] Endrin administered in the diet except where otherwise indicated

[b] Endrin administered by oral intubation

[c] Found dead in the wild

No 12-ketoendrin was detected in the body of the second hawk but there was 0.63 mg endrin/kg. These results suggest that endrin residues may be the most reliable indicator of lethality in birds.

Endrin has been suspected of killing birds and other animals in treated fields and in areas reached by run-off from these fields. Stickel et al. (1979b) investigated the residues of endrin in four species of birds from the Passeriforme order: grackles, Quiscalus quiscula; redwinged blackbirds, Agelaius phoeniceus; cowbirds, Molothrus ater; and starlings, Sturnus vulgaris. Birds were trapped and placed in large outdoor cages for months before being used. There was one cage each of 15 male starlings, 14 female starlings, 20 male cowbirds and 18 female cowbirds. Grackles were divided into several groups totaling 21 males and 23 females. For these Passeriforme birds, endrin was dissolved in corn oil and blended with feed at 10 ppm dw. Two bald eagles (Haliaeetus leucocephalus) were given horse meat containing 20 ppm endrin. Two female mallards (Anas platyrhynchos) were fed pellets containing 10 ppm endrin dw; 15 male mallards were placed on a dosage of 20 ppm endrin in the feed. After receiving endrin contaminated food, food consumption stopped almost immediately. By day 3 of exposure, Passeriforme birds were attacking and eating weakened cage mates. Tremors were not seen but convulsions were common. Most passerine birds died within 9 days; survivors were then sacrificed. In passerine birds, residues in brain tissue of at least 0.8 mg endrin/kg ww were found in dead birds; birds which survived had brain tissue levels of 0.6 mg endrin/kg ww or less (see Table V-4). At necropsy, tissues appeared normal indicating that birds died of neurotoxicity. Many birds also evidenced "hemorrhagic enteritis," a phenomenon also observed in rats according to Stickel et al. (1979b). The two bald eagles died at 13 and 20 days with doses of 20 ppm endrin; endrin concentrations in brain tissue were 1.2 and 0.92 mg/kg ww. Two females were sacrificed after 1 month of feeding with a diet containing 10 ppm endrin; brain residues were 0.54 and 0.77 mg endrin/kg ww. Ten male mallards died (time not reported) and five were sacrificed; residues in brain tissue of dead mallards ranged from 0.62-1.37 mg endrin/kg ww; in birds which were sacrificed, brain tissue levels ranged from 0.34-0.84 mg endrin/kg ww. No 12-ketoendrin residues were detected, except for one bird which had eaten an endrin-contaminated rodent.

Thus, birds with different food sources can be subject to endrin intoxication. Bald eagles, for example, may ingest rodents contaminated with pesticides. Stickel et al. (1979b) also reported residues of endrin in the brains of fish-eating white pelicans (11) that died in the wild; analysis of brain tissue indicated that 9 of the 11 died of endrin poisoning with tissue levels ranging from 1.3-2.7 mg endrin/kg ww. Some of these data are reported in Table V-4.

The data of Stickel et al. (1979b) may be criticized on the grounds that the endrin dose provided is a toxic one since food consumption ceased immediately. However, brain levels above 0.6-0.8 mg endrin/kg ww appeared to signify a lethal endrin exposure. Furthermore, 12-ketoendrin found in brains of birds would signify that the birds had eaten mammals which already had appreciable 12-ketoendrin residues.

Enzyme Activity. A comparative study was conducted to assess the contribution of the hepatic microsomal MFO system to a 7-fold difference in susceptibility to the lethal effects of endrin in endrin-resistant and susceptible pine voles, Microtus pinetorum (Hartgrove et al., 1977). ICR white mice were also used to provide a species comparison. Resistant pine vole colonies were established by mating survivors of a single oral dose of endrin (20 mg/kg bw). Susceptible colonies were derived from live-trapped animals and a 7-fold difference in susceptibility was determined by administering 2 mg/kg bw to randomly selected groups of voles. Oral LD_{50} values in mg endrin/kg bw were estimated for each strain: resistant voles, 18.8; susceptible voles, 2.6; ICR white mice, 12.3. The number of animals per group from which liver microsomes were prepared ranged from 3-19. Before sacrifice, animals were administered one oral dose of endrin at levels of 0.5, 2.0, 4.0, 10 or 20 mg/kg bw for resistant pine voles and 0.5 or 4.0 for susceptible pine voles and 4.0, 10 or 20 mg/kg bw for mice. The period of time between dosing and sacrifice was not reported. Substrates used in microsomal assays were ethylmorphine, aniline and benzo(a)pyrene. Ethylmorphine is a type I-binding substrate, while aniline is hydroxylated by the microsomal system; benzo(a)pyrene and endrin are both type I-binding and hydroxylating agents.

Results of the Hartgrove et al. (1977) study indicate the concentration of cytochrome P-450 (nmol/mg protein) in untreated pine voles was significantly greater (21%) in the resistant strain than in the endrin-susceptible strain. Even though the concentrations of cytochrome P-450 differed significantly in untreated pine voles, microsomal activity was not significantly different between endrin-resistant and endrin-susceptible pine voles for ethylmorphine N-demethylation, aniline hydroxylation or ^{14}C-benzo(a)pyrene disappearance. These data do not support a major involvement of microsomal activity in the resistance phenomenon. However, a species difference was observed in endrin-dosed animals. The rate of ethylmorphine N-demethylation was decreased by endrin treatment in pine voles but increased (>100%) in white mice. The rate of aniline hydroxylation was increased in both pine voles and mice but the increase in mice was much greater. Benzo(a)pyrene disappearance was significantly increased and 3-hydroxylation of benzo(a)-pyrene significantly decreased in endrin-treated animals which was suggestive of an alteration in the oxidative pathway. The concentration of cytochrome P-450 was unchanged after endrin dosage of pine voles but was significantly increased in white mice.

In contrast, microsomal preparations from female guinea pigs injected i.p. with endrin (3 mg/kg bw/day in safola oil) for 3 successive days exhibited decreased levels of cytochrome P-450 (Pawar and Kachole, 1978). _In vitro_ studies with endrin as a substrate may clarify the role of _in vivo_ pretreatment. Apparently _in vitro_ microsomal assays have not been attempted because of solubility problems and the inability to obtain metabolite standards.

Female guinea pigs were chosen for a study of the effects of endrin on hepatic and renal microsomal electron transport because of their sensitivity to the toxic effects of the pesticide (Pawar and Kachole, 1978). Six animals (600-650 g) were injected i.p. with endrin (3 mg/kg bw/day in safola oil) for 3 successive days; six control animals were injected with an equivalent amount of oil. Microsomes were prepared from liver and kidney tissue 24 hours after the third injection. The liver weights of endrin-treated animals were significantly increased and microsomal protein content was decreased. Kidney weight and renal microsomal protein were not affected. Decreased NADPH-linked aminopyrine N-demethylation was attributed to decreased levels of cytochrome P-450. Endrin treatment increased *in vitro* NADH-mediated aminopyrine N-demethylation and the authors suggested that the concomitant increase in cytochrome b_5 was responsible for the increased flow of electrons. A significant increase in lipid peroxidation in hepatic microsomes was observed when NADPH, NADPH + NADH, or ascorbate was the electron donor. NADH alone slightly decreased lipid peroxidation. In renal microsomal preparations, endrin treatment caused a gross increase in lipid peroxidation using various electron donors.

Four chlorinated hydrocarbons including endrin were tested for their possible interference with heme synthesis in Japanese quail, a species chosen because of high sensitivity to chlorinated organics as determined by urinary porphyrin concentrations (Nagelsmit et al., 1979). There was no indication that endrin was porphyrinogenic (1-3 or 5 mg/kg bw/day for 3 days given orally in a capsule), which suggested that urinary porphyrin would not reflect endrin exposure in exposed humans.

Endrin is one of five cyclodiene insecticides reported to inhibit beef heart and rat brain mitochondrial (oligomycin-sensitive) Mg^{2+}-ATPase activity *in vitro* (Mehrotra et al., 1982). In preparations of rat brain, activity was inhibited ~12% at 60 μM and 32% at 120 μM. Activity in beef heart mitochondrial preparations was inhibited ~21% at 20 μM and 38% at 100 μM. The addition of 120 μM endrin did not increase inhibition.

The oligomycin-sensitive Mg^{2+}-ATPase catalyzes ATP synthesis in mitochondria by oxidative phosphorylation. Inhibition of this enzyme results in decreased production of ATP and reduces the availability of ATP to $Na^{+}K^{+}$-ATPase which is the active sodium pump in the CNS, heart, and other tissues. Rat brain synaptosomal $Na^{+}K^{+}$-ATPase was slightly inhibited by endrin but the decreased activity was not concentration dependent. Oligomycin-insensitive Mg^{2+}-ATPase activity in preparations of rat brain synaptosomes and beef heart mitochondria was not inhibited by endrin at concentrations up to 120 μM. These data do not explain the greater in vivo toxicity of endrin in comparison with other cyclodiene pesticides.

Other Effects

Genotoxicity was not elicited by a variety of organochlorine pesticides including endrin tested in vitro in a hepatocyte primary culture DNA repair assay using hepatocytes from male Fischer F344 rats (300-375 g), CD-1 mice (25-35 g) and Syrian hamsters (85-130 g) (Maslansky and Williams, 1981). The potent procarcinogen, dimethylbenzanthracene, was the positive control and DMSO was the solvent control. The lack of endrin-induced genotoxicity agrees with the negative mutagenicity in sensitive microbial assays (see Mutagenicity Section).

Subacute Effects of Endrin

In a subacute study, Treon and Cleveland (1955) fed groups of 5 male and 5 female rats diets containing endrin. Concentrations in the diet of 50 and 100 ppm were lethal in a few weeks and the average survival of females (64.7 weeks) ingesting 25 ppm in the diet was less than that of males (86.1 weeks).

Diffuse degenerative changes were observed in the livers and kidneys of all fatally poisoned animals. In a second study, rats (5/sex/group) received 25, 50 or 100 ppm in the diet for 4 months. In the 50 ppm group, 2/10 animals survived while 3/10 survived from the 25 ppm group after 4 months. The average food consumption of endrin-fed rats was also less than that of control groups. In these studies, the serum alkaline phosphatase values fell initially, but at the end of the 4-month exposure the phosphatase values were higher among rats ingesting endrin than in control animals.

Treon et al. (1955) also studied the effects of endrin doses given in chow to dogs. Concentrations of 10-50 ppm dog chow were lethal and more than half of those fed a diet containing 5-8 ppm died. All dogs survived when their diets contained <3 ppm endrin (82-week study). Observations in survivors included increased organ-to-body weight ratios for the liver, kidney and brain. Dogs fatally poisoned were found to have diffuse degenerative lesions in the brain, heart, liver and kidneys, together with pulmonary hyperemia and edema.

In the only reported subacute study involving dermal exposure (Treon et al., 1955), three female rabbits/group were exposed to 100-mesh, dry endrin powder 75 or 150 mg (equivalent to 67-91 mg/kg bw/day at the high-dose and 20-42 mg/kg bw/day at the low-dose) under a rubber sleeve 2 hours daily, 5 days/week. In the high-dose group the rabbits died after 19, 19 and 25 applications. At the low-dose 1 of 3 died after the 40th application.

Nelson et al. (1956) fed diets containing 0, 1, 5, 25, 50 and 100 ppm in the diet to adult Sprague-Dawley rats (5/sex/group) for 16 weeks. All rats receiving 100 ppm died within the first 2-week period. Mortality rates for male rats were significantly greater (40%) at the 5 ppm dose than for female rats (0%). Serum alkaline phosphatase levels were also significantly higher and there was loss of weight in all rats consuming endrin compared with control animals. Hypersensitivity to sound, touch and pressure stimuli was noted in all treated rats. Convulsive spasms were manifested only in rats receiving the 25, 50 or 100 ppm doses.

Cattle and sheep were not affected by 5 ppm in the feed ingested over a 112-day period (Radeleff, 1956). Chickens (7 days old) were not made excitable by a ration containing 1.5 and 3 ppm endrin for 42 days. This was not so for concentrations of 6-12 ppm endrin; decreased weight gains were also shown at these concentrations (Sherman and Rosenberg, 1954).

A sex difference in the metabolism of endrin by rats may account for the difference observed in the response of CFE strain rats to the pesticide (Hutson et al., 1975). Six male and six female rats were dosed by stomach tube with 0.5 mg of endrin in 1 mℓ of arachis oil and housed in metabolism cages for 3 days to study the detoxication and bioactivation of endrin. Residues were higher in females than in males and were composed mainly of unmetabolized endrin. As detailed in Chapter III, the formation of 12-ketoendrin was shown to be related to the acute toxicity of endrin in rats.

Feeding studies were conducted to estimate the maximum tolerated doses of endrin in Osborne-Mendel rats and B6C3F$_1$ mice for a National Cancer Institute study of carcinogenicity (NCI, 1979). Endrin was first dissolved in acetone and then added to the feed. Corn oil was added to all feed (2%

of final weight of feed) as a dust suppressant. Five males and five females were given food with or without endrin for 6 weeks, followed by observation for 2 weeks.

For rats, endrin was added to the feed in 2-fold increasing concentrations, ranging from 2.5-80 ppm (NCI, 1979). There were no deaths at 10 ppm and mean weight gains were not different from controls. At 20 ppm, one animal of each sex died, but weights of survivors were not significantly affected. Thus, the maximum subacute tolerated dose was ~15 ppm.

In the same 1979 NCI subacute study, mice were given feed containing from 2.5-20 ppm endrin. At 10 ppm, 3 males and 4 females died in the group of 10 mice. No mortality occurred in the 5 ppm group; mean weight gains were comparable with that of controls. The maximum subacute tolerated dose was thus ~5 ppm. In these subacute exposures, increased mortality was the only toxic effect reported other than hyperexcitability in male mice receiving >5 mg/kg diet.

Chronic Effects

In a series of experiments, Treon et al. (1955) explored the effects of endrin ingestion in a number of species including rats, rabbits and dogs. Included in this study was the only report found of an inhalation exposure of animals to "vapors" of endrin (Table V-5). No convulsions were reported among this group of animals. Pathological findings were similar to those observed following other routes of administration.

TABLE V-5

Mortality of Animals Exposed to 0.36 ppm (5.62 mg/m^3) Endrin "Vapor"[a,b]

Species	No. of Exposure (days)	No. Dead/ No. Exposed	Daily Inhalation Volume (m^3/day)	µg Endrin[c] (7-hour day)
Cat	130	0/1	0.15	0.25
Guinea pig	130	0/2	0.074	0.12
Hamsters	101-130	0/2	0.037	0.061
Rats	130	0/3	0.26	0.43
Rabbits	118	2/4	1.6	2.6
Mice	107	1/3	0.05	0.082

[a] Source: Treon et al., 1955

[b] Exposed by inhalation 7 hours/day, 5 days/week for 185 days

[c] The original paper does not provide any weight data for these species in these experiments.

In chronic studies of endrin toxicity, the insecticide was dissolved in ethyl alcohol and added to pelleted Purina Fox Checkers (Treon et al., 1955). Groups of 20 male and 20 female rats were given diets containing 1 or 5 ppm endrin. At 80 or 106 weeks no difference was noted in the survival of treated and untreated animals. At 5 ppm there was an increase in liver-to-body weight ratio in males and an increase in kidney-to-body weight ratio in female rats. The NOEL was determined to be 1 ppm diet.

Beagle dogs (4/group) were administered 1, 3, 4, 5 and 8 ppm endrin in the diet for 18-19 months (Treon et al., 1955). At 8 ppm, two of four dogs died, and one of four dogs died at both 4 and 5 ppm. Animals fed diets containing $\geq$4 ppm did not grow normally. Concentrations of 1 or 3 ppm had no effect on growth. At autopsy, dogs fed at the 3 ppm level exhibited enlarged kidneys and hearts. Other organ weight-to-body weight ratios were not significantly different from those seen in control animals. Another study was conducted on groups of 7 male and 7 female dogs fed dietary levels of 0.1, 0.5, 1, 2 and 4 ppm endrin for 2 years (Treon et al., 1955). No deaths occurred which could be related to treatment; weight gain and food consumption were unaffected. Convulsions were seen in one female and two males ingesting 4 ppm and in one female fed 2 ppm. Histopathologic examination of tissues revealed slight changes in hepatocytes. At 1 ppm, no histologic changes were found.

Chronic exposure of Sprague-Dawley rats to oral doses of endrin in peanut oil 5 days/week for 7 months was directed towards investigating the use of the electroencephalogram (EEG) as an indicator of exposure (Speck and Maaske, 1958). Groups containing 20-60 animals were given 0.8, 1.7 or 3.5 mg endrin/kg bw. Animals drank the exposing solution readily from a feeding tube fitted with a syringe. After 1 week at 3.5 mg/kg, 4/30 had died and 16/26 had convulsions; EEG recordings revealed scattered spikes in 23/26 survivors. Respiration and heart rate of endrin-treated animals were increased. Convulsions were preceded by a period of hyperventilation. After 2 weeks of exposure to endrin, the rats had normal EEGs. At 3 months, animals became increasingly susceptible to audiogenic convulsions and at 7 months convulsions could be induced easily with auditory stimuli. At this time no spike activity was seen in EEG recordings. This lack of EEG findings during convulsions after chronic ingestion suggests that peripheral mechanisms are involved rather than activity at a higher level of the CNS. EEGs did not appear useful as an index of toxicity except during an initial phase of high chronic exposure or acute exposure.

Deichmann et al. (1970) conducted a chronic study for the primary purpose of providing information on the possible carcinogenicity of endrin, aldrin and dieldrin. Carcinogenic outcomes of chronic studies are reported in the Carcinogenicity section. Endrin dissolved in corn oil was added to ground Purina rat chow and administered to Osborne-Mendel rats (50 males and 50 females) at 1, 3 or 6 ppm for 10 weeks and at 2, 6 or 12 ppm until death or 31 months. There was no significant effect on mean body weight or weight gain in endrin-treated rats. Two hundred rats (100/sex) were fed an uncontaminated diet. No mention was made whether corn oil was added to the control diet. Signs of toxicity observed during the course of the experiment were limited to episodes of tremors and clonic convulsions with "outcries." These signs were dose related; however, the statement was made in general for all three insecticides. The mean survival rate for 12 ppm endrin-treated male rats was 17.6±6.9 months, and for 2 ppm treated rats, 18.1±4.9 months; mean survival for control rats was 19.7±4.8 months (statistical analysis not reported). The mean survival of female rats was about the same or slightly longer. Liver-to-body weight ratios were not significantly different from those observed in control animals. Histologic changes in the livers of rats fed endrin (2, 6 or 12 ppm) were similar to those receiving the control diet with the exception of a moderate increase in the incidence of centrilobular cloudy swelling; there was also an increase in cloudy swelling of the renal tubular epithelium.

The focus of Reuber's (1978) chronic study of endrin ingestion in rats was also the potential carcinogenicity of the insecticide. Each group, containing 24 male and 24 female Osborne-Mendel rats (22 days of age), ingested 0.1, 1.0, 5, 10 or 25 ppm endrin in the diet. The statement that, "endrin was dissolved in 1% corn oil and incorporated into ground commercial laboratory meal," was probably meant to convey that endrin was dissolved in corn oil and added to the diet at 1% dw. Within 1 week, one-half of the rats ingesting 25 ppm endrin were dead. A new group (32-day-old rats) was started on a dose of 25 ppm; the average survival time was reported to be 98.7 weeks with a range of 77-104 weeks. The average survival time of control animals was 94.8 weeks, range 66-104 weeks (statistical analysis not reported). These data suggest that younger animals are more susceptible to the toxic effects of endrin. However, toxicity in younger animals may have been a function of the lower body weight. A greater number of male rats ingesting endrin developed interstitial nephritis (chronic renal disease) than female rats. The incidence and severity of renal disease was related to dosage with the exception of male rats ingesting 5 ppm endrin.

The NCI (1979) conducted a chronic study with Osborne-Mendel rats and B6C3F$_1$ mice to determine the possible carcinogenicity of endrin. Endrin was added to feed as described in subacute effects. Fifty animals of each sex constituted a treatment group of rats or mice. Ten animals of each sex were matched controls and data from 40 or 50 untreated animals from similar bioassays were pooled for statistical evaluation.

Groups of rats (100 each) were administered one of two doses of endrin for 80 weeks (NCI, 1979), and then observed until survivors were sacrificed at 110-114 weeks. Male rats received 2.5 or 5 ppm endrin in the diet; initial doses for females of 5 or 10 ppm endrin in the diet were not well tolerated and were reduced during the study to 2.5 and 5 ppm. There was neither a significant effect on mean body weight nor a significant dose-related trend in mortality. Clinical signs usually associated with aging were observed earlier in dosed rats than in controls: alopecia, diarrhea, epistaxis, tachypnea, pale mucous membranes, hematuria, rough hair coats and dermatitis.

Mice were administered endrin in the diet for 80 weeks and observed until sacrifice at 90-91 weeks. Initial doses of 2.5 or 5 ppm were not well tolerated by male mice and were reduced to 1.2 and 2.5 ppm (NCI, 1979).

The TWA was calculated to be 1.6 and 3.2 ppm. Female mice were kept at the 2.5 or 5 ppm level. Mean body weights were similar to corresponding controls and there was no dose-related trend in mortality in female mice. Survival was decreased in high-dose male mice; a large number of the low-dose males died following the accidental overdose at 66 weeks and survival could not be determined. Before the overdose, clinical signs included alopecia, diarrhea, epistaxis, rough hair coats, tachypnea, hematuria and discolored urine. After about 4 months, all of the high-dose male group appeared hyperexcitable, and doses for males were lowered as indicated above. Lowering the dose did not change the hyperexcitable behavior in the majority of the group. In the last half of the first year, clinical signs were apparent: abdominal distension, alopecia and rough hair coats. Because of an error at week 66, excessive amounts of endrin were given to the 1.2 ppm dosed male mice which caused animals to be hyperexcitable until termination. Researchers determined that a rather fine line exists between endrin levels causing CNS toxicity and those virtually nontoxic.

Kreitzer (1980) determined whether behavioral effects would be produced by endrin at levels below those that produced overt signs of intoxication. Adult male bobwhite quail, Colinus virginianus, were fed endrin dissolved in propylene glycol and blended into feed at levels of 0.1 and 1.0 ppm. An equal amount of propylene glycol was added to the feed of controls. There were four controls and four birds at each treatment level for all tests that measured performance on nonspatial discrimination reversal tasks. Birds were dosed (beginning at the age of 3 days) for 138, 185 and 240 days before Tests 1, 2 and 3, respectively. The fourth test began after 267 days of dosing followed by 25 days of untreated feed, and the fifth test after 278 days of dosing followed by 50 days of untreated feed. Endrin-treated birds made from 36-139% more errors than did controls ($p<0.025$). The difference between acquisition error scores of controls and treated birds increased exponentially over the first four tests. The 0.1 ppm diet dosed birds made significantly more errors than the 1.0 ppm birds after reversal of black and white patterns used for discrimination to receive a reward. There was no explanation for this effect. Endrin effects were reversed after 50 days of untreated feed. The principal effects of endrin was to impair the birds' ability to solve a novel problem. Mean brain residues in endrin-treated birds were 0.075 mg endrin/kg ww for the 0.1 ppm dose and 0.35 mg endrin/kg ww for the 1.0 ppm dose.

Jager (1970a) published an extensive review of the epidemiology and toxicology of long-term exposure to aldrin, dieldrin, endrin and telodrin. In a discussion of endrin toxicity in animals, Jager concluded that even though endrin is a stereoisomer of dieldrin, it differs from dieldrin in the following respects: higher acute toxicity, more rapid metabolism, and less persistence in vertebrates. The endrin LD_{50} varied with the vehicle and experimental species used, endrin being 4-5 times more acutely toxic than dieldrin. The dietary NOEL for endrin in chronic feeding studies in the rat and the dog was 1 ppm endrin in the diet.

Interactions

Ludke (1976) demonstrated that prior treatment with a closely-related insecticide can increase bird mortality. Fourteen-week-old male and female white quail (*Colinus virginianus*) were divided into four groups; four birds constituted the control group. All groups were fed turkey maintenance mash with 1% (w/w) propylene glycol mixed in the diet. Pesticides were dissolved in propylene glycol and mixed into the diet. Twenty-eight birds received 10 ppm technical chlordane in the diet for 10 weeks and 20 of these were then fed 10 ppm 98% pure endrin in the diet for 6-10 days. A fourth group (N=20) was fed 10 ppm endrin in the diet. No mortality occurred in the control group nor in the group fed chlordane alone. For endrin-fed birds, mortality occurred on days 1 (1 bird), 6 (7), 9 (5) and 10 (2). For the chlordane-endrin-treated groups, mortality occurred on days 3 and 6-10 (14 birds) of endrin exposure, and survivors were sacrificed on days 9 and 10 of endrin exposure. All surviving birds treated with endrin alone or chlordane-endrin lost weight and showed depleted lipid content in the carcasses (Table V-6). Control and chlordane-treated birds showed no significant decreases. Birds that survived exposure to chlordane-endrin or endrin alone had lower brain residues of endrin than the dead birds. Birds dying of endrin poisoning alone had brain residues ranging from 0.34-1.84 mg endrin/kg ww (survivors = 0.28-0.62 mg endrin/kg ww). In chlordane-endrin-treated birds, the dead birds contained 0.17-1.25 mg endrin/kg brain, whereas the survivors had 0.14-0.56 mg/kg brain. The latter two groups differed at $p<0.10$. Dead or moribund birds treated with the two pesticides contained significantly lower ($p<0.025$) endrin brain residues than the corresponding birds treated with endrin alone. Thus, birds may be more vulnerable to a toxicant if the bird already carries a body burden of one or more closely related chemicals. In this study, mortality from endrin alone was associated with as little as 0.34 mg endrin/kg brain.

TABLE V-6

Weight Loss and Lipid Content (Mean % ± S.E.) of Quail Carcasses After Technical Chlordane, 98%-Pure Endrin, and Chlordane-Endrin Treatments*

Treatment		Condition	No.	% Lipid	% Weight Loss
Chlordane	Endrin				
None	none	S	4	4.69±0.77	0
10 ppm diet: 10 weeks	none	S	4	3.45±0.56	0
None	10 ppm diet: 6-10 days	D	13	0.43±0.14	32.2±2.4
		M	1	0.73	68.6
		S	3	2.73±0.97	14.7±1.1
10 ppm diet: 10+ weeks	10 ppm diet: 6-10 days	D	12	0.39±0.06	31.4±3.0
		M	3	0.27±0.04	37.2±11.7
		S	3	2.78±1.29	19.1±3.5

*Source: Ludke, 1976

S = Sacrificed, no apparent signs of toxicity; D = dead; M = moribund or sick (reduced activity and lowered appetite)

Meena et al. (1978) investigated endrin-induced toxicity in normal rats and rats irradiated with gamma radiation by dividing 128 male albino rats (150-200 g) into four equal groups. The control group received groundnut oil i.p.; group 2 received a single i.p. injection of 10 mg endrin/kg bw in groundnut oil; group 3 served as irradiated controls (900 rads); group 4 received 10 mg endrin/kg bw 0.5 hours after irradiation. In both normal and irradiated rats, endrin caused a significant increase in SGOT, SGPT and ATPase; acid and alkaline phosphatase, succinic dehydrogenase and glucose-6-phosphatase decreased significantly during varying periods of 2-48 hours after treatment. In irradiated rats given endrin, the changes appeared earlier and were more pronounced than in normal rats given endrin alone, except in the case of ATPase where endrin appeared to neutralize the effect of radiation on the mitochondrial membrane. The study indicated that endrin leads to injury of liver and kidney tissues, and that this may occur sooner after gamma irradiation of rats.

Teratogenicity and Reproductive Effects

Mammals. Two studies of endrin toxicity in rodents were conducted in the 1960's at doses which were toxic to the mother. Endrin was added to the feed of Sprague-Dawley rats (Green, 1969) and of CFW Swiss mice (Good and Ware, 1969) at 5 ppm and fed to the animals before and during gestation (Table V-7). Green (1969) reported increased early resorption of embryos and Good and Ware (1969) reported increased maternal mortality and significantly smaller litter size, also indicating increased resorption.

TABLE V-7

Teratogenicity and Reproductive Studies Performed with Endrin in the 1960's

Species	Sex	Dose (ppm)	Feeding Procedure	Effects	Reference
Sprague-Dawley rats	females	5	60 days before and during gestation	Increase in resorptions	Green, 1969
CFW Swiss mice	males and females	5	4 months before and during gestation	Parental mortality (1/3) Significantly smaller litter size	Good and Ware, 1969
Deer mice (*Peromyscus maniculatus osgoodi*)	14 parental pairs/dose	2 4 7	At intervals over 7-month period	Parental mortality Significant decrease in survival of offspring at 21 days	Morris, 1968

At about the same time, Morris (1968) studied the effects of endrin feeding on field-captured deer mice (Peromyscus maniculatus osgoodi) parental survival, fertility, litter size and survival of young to weaning (see Table V-7). Reproductive performance was recorded for 6 months before a 7-month feeding program was initiated (0, 1, 2, 4 and 7 ppm endrin in the diet). Postnatal mortality of the young appeared to be the major effect of endrin on the offspring of deer mice; however, soft and skeletal tissues were not examined for the incidence of malformations. Survival of parents was significantly decreased at endrin levels ≥ 2 ppm.

A single oral dose of endrin, 5 mg/kg bw (1/2 LD_{50}), administered by intubation to pregnant Syrian golden hamsters, caused a marked and statistically significant increase in fetal deaths in animals treated on day 7 or 8 of gestation (Ottolenghi et al., 1974). In these studies (Table V-8), two control groups were used, one group receiving the corn oil vehicle and a second group receiving no treatment. Comparisons of litters from pesticide treated hamsters were made with the corn oil-treated group for evaluation of the incidence of embryocidal and teratological effects by using the Mann-Whitney U-test. Dunnett's multiple comparisons test was used to evaluate differences in fetal weight. A statistically significant increase in the incidence of fused rib and cleft palate ($p<0.01$) occurred in litters from dams treated on day 7, 8 or 9 and sacrificed on day 14 of gestation. A significant increase in open eye and webbed foot occurred only in litters from dams treated on day 8. Fetal weight was reduced in all treated litters. The association of webbed foot and open eye with low fetal weight suggests that these effects may be an expression of growth retardation (Ottolenghi et al., 1974).

TABLE V-8

Reproductive Effects of Endrin for Studies Performed Since 1970

Species	Route of Adminis-tration	Dose (mg/kg/day)	Vehicle	Day of Gestation	No. of Litters	Effects	Reference
Golden syrian hamsters	oral gavage	5	corn oil	7 8 9	7 21 8	Fetal death (32% of implantations), growth retardation, congenital abnormalities in 28% of fetuses treated on day 8: open eye, 22%; webbed foot, 16%; cleft palate, 5%; cleft lip, 1%; fused ribs, 8%	Ottolenghi et al., 1974
Golden syrian hamsters (LVG strain)	oral gavage	>0.75	corn oil	5-14	19	Marked maternal toxicity; hypoactivity, tremors, reduced weight gain, lethality; fetal toxicity; increased mortality, reduced fetal weight, reduced skeletal ossification	Chernoff et al., 1979
Golden syrian hamsters (LVG strain)	oral gavage	≥1.5	corn oil	5-14	21	Significant maternal lethality and weight reductions. meningoencephaloceles in fetuses of two litters	Chernoff et al., 1979
Golden syrian hamsters	oral gavage	>1.5	corn oil	8	34	Meningoencephaloceles; no overt embryolethal or maternotoxic effects	Chernoff et al., 1979
Golden syrian hamsters	oral gavage	≥5.0	corn oil	8	50	Fused ribs and meningoencephaloceles; no overt embryolethal or maternotoxic effects	Chernoff et al., 1979
Golden syrian hamsters	oral gavage	1.5	corn oil	5-14	13	Persistent elevation of locomotor activity in offspring; nonlocomotor behavior of offspring unaffected; 57% of dams died during dosing period.	Gray et al., 1981
CD rats	gastric intubation	0.075	corn oil	7-20	14	No effect on maternal weight gain or fetus	Kavlock et al., 1981
CD rats	gastric intubation	0.15	corn oil	7-20	27	No effect on maternal weight gain or fetus	Kavlock et al., 1981
CD rats	gastric intubation	0.3	corn oil	7-20	29	Significant decrease in maternal weight. No effect on fetus.	Kavlock et al., 1981
CD rats	gastric intubation	0.450	corn oil	7-20	12	87% decrease in maternal weight gain, no apparent effect on the fetus	Kavlock et al., 1981

TABLE V-8 (cont.)

Species	Route of Adminis-tration	Dose (mg/kg/day)	Vehicle	Day of Gestation	No. of Litters	Effects	Reference
CD rats	oral gavage	0.075 0.15 0.30	corn oil	7 through day 15 of lactation	13 13 5	Pups 30% more active in the mazes than controls or 0.075 mg/kg endrin dose groups; at 90 days of age, no endrin-induced differences were apparent; did not affect pup survival or growth.	Gray et al., 1981
CD-1 mice	oral gavage	2.5	corn oil	9	10	Congenital abnormalities: open eye; cleft palate	Ottolenghi et al., 1974
CD-1 mice	gastric intubation	0.5	corn oil	7-17	31	Maternal liver enlargement	Kavlock et al., 1981
CD-1 mice	gastric intubation	1.0	corn oil	7-17	32	Reduced maternal weight gain; decrease in fetal weight and skeletal and visceral maturation	Kavlock et al., 1981
CD-1 mice	gastric intubation	1.5	corn oil	7-17	12	Maternal lethality; no teratogenic effect or embryo lethality; decreased locomotor activity, reduced weight gain in pups; activity levels depressed after first and third doses but no significant difference after tenth dose.	Kavlock et al., 1981
CD-1 mice	gastric intubation	2.0 single dose	corn oil	7-17	2	No dose-related evidence of open eyes and cleft palate	Kavlock et al., 1981
CD-1 mice	gastric intubation	2	corn oil	8-12	17	Reduced maternal weight, reduced fetal weight	Chernoff and Kavlock, 1982

Ottolenghi et al. (1974) also examined the effects of orally administered endrin in corn oil (day 7, 8 or 9 of gestation) on the fetuses of CD-1 mice (see Table V-8). The frequency and gravity of defects produced by a single dose of 2.5 mg/kg bw (1/2 LD_{50}) administered to mice on day 9 of gestation were less pronounced than those seen in hamsters at 5 mg/kg. Abnormalities included an increased incidence of eye opening ($p<0.5$) and a low occurrence of cleft palate. No significant effects were found with regard to fetal survival or fetal weight.

A single dose of endrin in corn oil administered to Syrian golden hamsters by oral gavage on day 8 of gestation produced meningoencephaloceles at doses above 1.5 mg/kg bw and fused ribs at doses above 5.0 mg/kg (see Table V-8). Open eyes, cleft palate and webbed foot were not observed. No significant effects were noted in either maternal mortality and weight gain or fetal mortality and weight gain. In a multiple dose study, the administration of endrin on days 5-14 of gestation produced maternal lethality at doses $\geq$1.5 mg/kg bw/day. Fetal toxicity (including increased mortality, reduced fetal weight and reduced skeletal ossification) resulted at doses above 0.75 mg/kg/day (see Table V-8). Endrin crossed the placenta and was identified in the fetus. 12-Ketoendrin was found in both mother and fetus but not quantified (Chernoff et al., 1979).

In the hamster, exposure to endrin in corn oil at 1.5 mg/kg bw/day on days 5-14 of gestation produced a significant elevation in locomotor activity of offspring that was still present at 125 days of age (see Table V-8).

Nonlocomotor behavior of the offspring (including rearing in the open field, running wheel activity and mounting) were not altered by treatment. Dams were markedly hypoactive using the same testing conditions in which the pups were hyperactive. More than half of the group receiving 1.5 mg/kg/day died. Rats exposed on days 7 through 15 of gestation to endrin at 0.15 or 0.30 mg/kg/day were 30% more active than controls before weaning but not as adults. These doses did not kill the dams or affect pup survival or growth. In this study, a dose of 0.075 mg/kg/day appeared to have no effect on behavior. Behavioral effects may be of special concern in view of the persistence of endrin in the environment and its capability for magnification in the food chain (Gray et al., 1981).

Kavlock et al. (1981) found that endrin was not teratogenic or embryolethal in the CD rat or CD-1 mouse when administered by gastric intubation at maternally-toxic dose levels throughout the period of organogenesis (see Table V-8). Adult female rats tolerated 2-3 times less endrin than did adult mice or hamsters, but the rat is the only one of the three species in which endrin did not induce fetotoxicity. The difference in fetal sensitivity was attributed to lower levels of 12-ketoendrin present in the rat fetus than observed in the hamster fetus.

Chernoff and Kavlock (1982) assayed 28 compounds of known teratogenic potential were assayed by an _in vivo_ teratology screening procedure (see Table V-8). Endrin was administered by oral gavage (2 mg/kg bw) to 25 gravid CD-1 mice on days 8-12 of gestation. Dams were allowed to give birth, and litter size and weight on postpartum days 1 and 3 were compared with concurrent controls. Results indicated significantly reduced maternal weight and reduced fetal weight on postpartum day 1.

A disastrous die-off of brown pelicans, which reduced the population from 400 to 250 birds, occurred in Louisiana in May and June 1975. Several months earlier, a die-off of ~100 white pelicans occurred near the same area. Shell thickness of pelican eggs from 1971 through 1976 averaged 6.7-13.5% less than the mean thickness for eggs collected before 1947. Statistical analysis of data on residues in eggs indicated that there were significant differences in DDT and DDE mean concentrations for several years but no pronounced trend. PCB residues remained essentially the same. Dieldrin residues increased significantly during the study; endrin residues increased significantly through 1975, and then dropped sharply in 1976. Endrin has been considered the major factor in the die-offs because endrin residues were detected in brains of several pelicans and because the die-off in 1975 coincided with the peak in endrin residues in pelican eggs. The effect of endrin on reproductive success is unknown, but the egg with the highest residues (1.47 mg/kg ww) contained an embryo that died while pipping (Blus et al., 1979).

On the basis of further studies, the critical level of endrin in brown pelican eggs was roughly estimated at $\geq$0.5 μg/. More exact determination was not possible because of the small population. Of the avian species studied, the brown pelican was the most sensitive to organochlorine contaminants, particularly DDE and endrin (Blus, 1982).

Mutagenicity

Endrin was one of 228 pesticides tested for mutagenicity in a Salmonella typhimurium reverse mutation assay using strains TA1536, TA1537, TA1538, TA98 and TA100 (Ames et al., 1975). Endrin was not mutagenic for any of the above bacterial strains, nor for Escherichia coli WP2 hcr. These in vitro assays were done both with and without addition of rat hepatic homogenates (S9) to supply mammalian metabolic enzymes (Moriya et al., 1983). The National Toxicology Program (U.S. DHHS, 1982) also reported endrin to be nonmutagenic for Salmonella, although no details of testing procedures were given. A third study utilized a modification of the standard reverse mutation assay wherein the Salmonella strains were streaked on agar plates poured so as to obtain a concentration gradient of the test compound. Endrin was not mutagenic for any of the above strains nor for the following: his G46, his C3076, or his D3052 (Probst et al., 1981).

Endrin exposure of primary rat or hamster hepatocytes did not result in increased unscheduled DNA synthesis (Probst et al., 1981; Williams, 1980). This nonreplicative DNA synthesis is regarded as an indicator of repair of DNA damage. Endrin (as well as DDT, mirex, kepone, hexachlorocyclopentadiene, heptachlor and chlordane) produced no increases over control numbers of mutants at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus when tested in adult rat liver epithelial cells (Williams, 1980; Telang et al., 1981).

Adult Drosophila were exposed to endrin by abdominal injection, and the Muller-5 test for recessive lethal mutation on the X-chromosome was done. The authors noted no positive responses for endrin or any other chlorinated pesticide tested (Benes, 1969)

In an abstract, Grant (1973) reported that among a number of organochlorine pesticides, endrin, aldrin, chlordane, dieldrin, DDT, heptachlor and lindane, all caused chromosome breakage. The organisms and dosage routes were not described. Dikshith and Datta (1973) reported the effects of endrin on rat chromosomes. Male rats, treated intratesticularly with 0.25 mg endrin (in saline) per testis, exhibited chromosomal aberrations in germinal tissue. Abnormalities included breaks, fragments, ring formation, stickiness and chromatin bridges.

Carcinogenicity

Endrin has been examined for carcinogenicity in mice (B6C3F$_1$, C57B1/6J, C3D2F1/J and C3HF strains), rats (Osborne-Mendel, Sprague-Dawley), and dogs (beagle and mixed breeds). Reuber (1979) has strongly claimed carcinogenicity for rats, and less strongly for other animal species, evidence accumulated to date remains somewhat conflicting since results have been negative for most studies. In studying mice and dogs, clear conclusions have been much more difficult to reach, owing to toxicity problems and the inadequate numbers in most investigations. The following studies are summarized in Table V-9.

The first study of endrin carcinogenicity was conducted by Treon et al. (1955). Endrin was administered to 28-day-old rats, 20 males and 20 females/group, in doses of 0, 1, 5, 25, 50 or 100 ppm endrin in the feed for 106 weeks. The 100 ppm dose approximated 10 mg/kg bw/day. Doses $\geq$25 ppm for females and $\geq$50 ppm for males resulted in significant mortality by 106 weeks so that few animals remained at these higher doses for pathological examination. Signs of overt toxicity (hypersensitivity to external stimuli,

TABLE V-9

Negative Studies of the Carcinogenic Potential of Endrin

Animal	Strain	No. in Group	Sex	Route	Carrier	Doses (ppm feed)	Study Duration (weeks)	Malignancy Information	Reference
Rat	NR	20 20	M F	oral (feed)	95% ethanol	0, 1, 5, 25, 50, 100	106	No excess	Treon et al., 1955
	Osborne-Mendel	50[a] 50[a]	M F	oral (feed)	corn oil	0, 1, 3, 6 (10 weeks) then 0, 2, 6, 12 ppm	116	Not considered carcinogenic	Deichmann et al., 1970
	Osborne-Mendel	50[b] 50[b]	M F	oral (feed, corn oil)	acetone	0, 2.5, 5.0 0, 3.0, 6.0	114 (80 weeks exposure)	Not carcinogenic	NCI, 1979
Mice	C57Bl/6J	100 100	M F	oral (feed)	95% ethanol	0, 0.3, 3.0	78	No excess	Witherup et al., 1970
	C3D2F1/J	100 100	M F	oral (feed)	95% ethanol	0, 0.3, 3.0	72	Not carcinogenic	Witherup et al., 1970
	B6C3F1	50[b] 50[b]	M F	oral (feed, corn oil)	acetone	0, 1.6, 3.2 0, 2.5, 5.0	90 (80 weeks exposure)	Not carcinogenic	NCI, 1979

[a] Control number was 100

[b] Control number was 10. Data from 40 pooled controls from other studies added for statistical analyses.

NR = Not reported

or occurrence of convulsions) were not evoked at doses ≤25 ppm. The authors reported that the incidence of neoplasia was no greater among experimental animals than among controls in the tissues studied (liver, kidney, brain, heart, adrenal gland, spleen, skin, lung, and other unidentified tissues). No primary data were presented. Subsequent independent assessment of histological specimens led to the report (Reuber, 1979) that one animal ingesting 25 ppm had a carcinoma of the pituitary and one ingesting 50 ppm a bronchogenic carcinoma. No malignancies were originally reported in untreated rats although these (and endrin-treated animals) were later reported to have developed benign tumors of the breast and reticulum sarcomas.

In addition to the above, three independent studies were conducted with the same rat strain (Osborne-Mendel) under similar conditions. Deichmann et al. (1970) found that animals ingesting endrin dissolved in corn oil and admixed with ground Purina chow developed malignant tumors; however, similar incidences occurred in control animals. In this study, Osborne-Mendel weanling rats, 50 male and 50 female per treatment and 100 male and 100 female per control group were administered 1, 3 or 6 ppm endrin in the feed for 10 weeks and then twice those concentrations until sacrifice, the time of which varied considerably (5-29 months). Male animals treated with final doses of 2, 6 or 12 ppm showed 15, 9 and 24% incidences, respectively, of malignant tumors, compared with 18% in controls. In females the corresponding incidence of malignancies was 21, 11 and 22%, with 24% in control animals. The predominant tumor type in both sexes in all groups was malignant lymphoma. In this study excess cancer incidence in animals ingesting endrin was not reported in the liver, endocrine organs or reproductive tissues, as was observed in the previous studies. The authors concluded that endrin fed for a lifetime to albino rats was neither tumorigenic nor carcinogenic.

TABLE V-11

Incidence of Malignant Tumors in Female Rats Ingesting Endrin[a]

Endrin Concentration (ppm feed)	No. Animals Examined	Liver		Lung Sarcoma	Mammary Gland		Other		Total Malignant Tumors
		Carcinoma	Sarcoma		Carcinoma	Sarcoma	Carcinoma	Sarcoma	
0	23	0	0	0	6	1	2[b]	0	9
0.1	23	0	1	0	10	2	0	1[c]	14
1	23	0	0	1	14	0	2[d]	1[c]	18
5	20	1	0	1	13	0	0	0	15
10	18	0	1	0	8	1	1[e]	0	11
25	19	1	0	0	1	2	5[f]	1[c]	10

[a] Source: Reuber, 1978

[b] Papillary adenocarcinoma, site unknown

[c] Uterus

[d] Thyroid and colon

[e] Adrenal cortex

[f] Four in thyroid and one in the adrenal cortex

overt signs of toxicity in the animals. Inherent difficulties are encountered when interpreting Reuber's (1978) report. Statistics were based on the number of animals with malignant tumors. From the data, the reader cannot justify the numbers reported in the text; also one animal may develop more than one lesion.

In a study by NCI (1979), 35-day-old male Osborne-Mendel rats were fed a diet incorporating endrin initially dissolved in acetone to a level of 2.5 or 5.0 ppm diet. Females (50) were fed a diet containing 0, 3.0 or 6.0 ppm technical grade endrin for 80 weeks and surviving animals were sacrificed at 111-114 weeks. There were 10 control rats of each sex. The tissues utilized for histopathology were the following: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, pancreas, stomach, intestines, kidneys, bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary and brain. Comparing incidences of malignant tumor formation in individual tissues between control and treated animals, the authors of the study concluded that endrin was not carcinogenic in either sex. Malignant tumors which were observed in two or more male animals per group (4% incidence in treated animals) were hematoma of the kidney (4% at the high dose), adrenal carcinoma (4% at the low dose), islet cell carcinoma of the pancreas (6% at the high dose) and fibrous histocytoma (4% at the high dose). The increased incidence of islet cell carcinomas in the high dose group was statistically significant compared with controls applying the Cochran-Armitage, but not the Fisher exact test. Cancer incidence at other sites was not statistically significant. In female animals, two or more animals had malignancies in the pituitary (4% at the low dose) and adrenal (14% at the low and 6% at

In a second Osborne-Mendel rat study reported by Reuber (1978), 22-day-old male and female rats, 24/group, ingested endrin admixed in corn oil with the diet (1%) for 104 weeks (0, 0.1, 1.0, 5, 10 and 25 ppm). Owing to high and early mortality in the highest concentration group, additional groups of animals ingesting this concentration were subsequently established. Some of the tissues studied on sacrifice were lung, spleen, kidney, heart, liver, pancreas, stomach, small intestine, colon, kidney, adrenals, thyroid, ovary, leg muscle, leg bone, bone marrow, bladder and prostate. In male rats, endrin induced hyperplastic nodules in the liver. For both nodules and "malignant lesions" (defined as the sum of carcinomas and sarcomas), endrin appeared most active at a dose of 0.1 ppm. The tabulated data were often confusing. The incidence of malignant hepatic neoplasia in males and females was relatively low (Tables V-10 and V-11). No malignant tumors in the liver were observed in control animals of either sex. In addition to developing liver lesions, endrin-treated rats of both sexes developed neoplasms at a number of other sites. In males these included reticulum cell sarcomas of the lungs and lymph nodes and some rare malignant tumors, as well as carcinomas of the thyroid and renal cortex. The observations showed no preferred cancer site (greater than two instances) although frequencies never exceeded 13% for a specific site at a given dose. In females, carcinomas and leiomyosarcomas of the mammary gland, stromal cell sarcomas of the uterine endometrium, reticulum cell sarcoma of the lung and hepatic Kupffer cell sarcoma were observed (see Table V-11). The preferred cancer sites in this study were the mammary gland, the thyroid and the uterus, in that order. On the basis of the above findings, the author concluded that endrin was a carcinogen. The data appear more conclusive for female rats than for male rats. Doses below 5 mg/kg appeared to elicit few

TABLE V-10

Incidence of Malignant Tumors in Male Rats Ingesting Endrin[a]

Endrin Concentration (ppm feed)	No. Animals Examined	Liver		Lung Sarcoma	Mammary Gland		Other		Total Malignant Tumors
		Carcinoma	Sarcoma		Carcinoma	Sarcoma	Carcinoma	Sarcoma	
0	15	0	0	0	0	0	0	0	0
0.1	16	2	0	1	0	1	4[b]	3[c]	11
1	18	0	0	0	0	1	1[d]	1[e]	3
5	18	0	0	0	1	0	0	0	1
10	20	1	1	0	0	1	0	1[f]	4
25	19	1	0	1	0	0	1[g]	2[h]	5

[a] Source: Reuber, 1978

[b] Two thyroid, adenocarcinoma (site unknown) and adrenal cortex

[c] Two in lymph nodes and one in the stomach

[d] Stomach

[e] Kidney

[f] Hemangioendothelial

[g] Thyroid

[h] Lymph node and osteogenic

the high dose but 11% in controls). None of these increased incidences were statistically significant, but the increases of pituitary adenomas, and combined increased incidences of adenomas and carcinomas of the adrenal were. The major defect in this study was the use of only 10 controls per gender.

The opposite conclusions to those made above were reached, however, by a later reviewer of this study (Reuber, 1979) after re-examination of the pathology slides, and based on comparisons of cumulated cancer incidences at different sites, i.e., endocrine and reproductive tissues, or control vs. treated groups. In males and females, increased cancer incidence compared with controls was thereby observed for both doses of endrin for endocrine organs (pituitary and adrenal glands) and the liver. In addition, females showed an increase in incidence of malignant tumors of the ovary, uterus and mammary gland. In males, the numbers of animals with malignant tumors (carcinomas and sarcomas) were 67% and 64% at the low and high doses, respectively, compared with 10% in the control groups. In females, the corresponding values were 74 and 82% compared with 40% in the control groups. In female rats, 74 and 67% of animals ingesting the low and high dose, respectively, had carcinomas of the endocrine organs, compared with 10% of untreated animals. In male rats, the corresponding incidences were 36 and 42% in treated and 10% in control animals. Statistically significant increases in carcinoma incidence in the pituitary (43% low-dose, 30% high-dose, 0% control) and adrenal glands (33, 31 and 0%, respectively) were observed in female rats at both endrin doses (Table V-12), and in the pituitary gland of males at the lower dose (29% compared with 0% in controls) (Table V-13). In female rats, 40 and 28% developed malignant tumors of the reproductive system at the low and high endrin doses, respectively, compared

TABLE V-12

Number of Osborne-Mendel Female Rats with Carcinomas[a]

Dose (ppm endrin in the diet)	Number Examined	Endocrine	Pituitary	Adrenal	Reproductive System	Liver	Total No. with Carcinomas
0 matched	10	1 (10%)[b]	0	0	1 (10%)	0	1 (10%)
Pooled	49	11 (23%)	6 (12%)	0	3 (6%)	0	5 (10%)
2.78	46	34 (74%)[c]	20 (43%)[d]	15 (33%)[e]	17 (40%)[f]	1 (2%)	29 (63%)[g]
5.56	46	31 (67%)[h]	14 (30%)[i]	14 (31%)[j]	13 (28%)[k]	4 (9%)	35 (76%)[l]
Low + high dose	92	65 (71%)[m]	34 (37%)[n]	29 (32%)[j]	30 (33%)[f]	5 (5%)	64 (70%)

[a] Sources: NCI, 1979; Reuber, 1979

[b] Percentage of animals examined with tumor of tissue specified

[c] $p<10^{-5}$, one-sided test

[d] $p<10^{-3}$, one-sided test

[e] $p<5\times10^{-6}$, one-sided test

[f] $p<3\times10^{-4}$, one-sided test

[g] $p = 2\times10^{-5}$, one-sided test

[h] $p<10^{-5}$, one-sided test

[i] $p = 2.7\times10^{-2}$, one-sided test

[j] $p<1.2\times10^{-5}$, one-sided test

[k] $p = 3.4\times10^{-3}$, one-sided test

[l] $p = 1.8\times10^{-2}$, one-sided test

[m] $p<10^{-7}$, one-sided test

[n] $p = 7\times10^{-4}$, one-sided test

TABLE V-13

Number of Osborne-Mendel Male Rats with Carcinomas[a]

Dose (ppm endrin in the diet)	Number Examined[b]	Endocrine	Pituitary	Adrenal	Liver	Total No. with Carcinomas
0 matched	10	1 (10%)	0	1 (10%)	0	1 (10%)
Pooled	49	5 (10%)	3 (6%)	1 (2%)	0	4 (8%)
2.5	45	17 (36%)	13 (29%)[c]	1 (2%)	1 (2%)	24 (53%)[d]
5.0	45	19 (45%)	7 (16%)	4 (9%)	2 (4%)	22 (49%)[d]
Low + high dose	90	36 (40%)	30 (22%)[e]	5 (6%)	3 (3%)	44 (49%)[d]

[a] Sources: NCI, 1979; Reuber, 1979

[b] Percentage of number examined

[c] $p = 0.003$, one-sided test

[d] $p<0.000,009)$ one-sided test

[e] $p = 0.001$, one-sided test

with 10% of control animals (see Table V-12). Hepatocellular carcinoma incidences observed in low and high-dose endrin-treated female rats, compared with controls, were 2, 9 and 0%, respectively, but were not statistically significant. The corresponding figures for male rats were 2, 4 and 0%, respectively and also not significant. Female rats therefore appeared to be more susceptible than male rats at the various target sites mentioned above. The incidences of benign tumors in male or female rats were not reported to be significantly different from values in controls or any endrin dose (Tables V-14 and V-15).

Re-evaluation of the tissue sections by Reuber (1979) thus has resulted in dramatically increased tumor incidences in both control and exposed groups. Reuber's criteria for classifying tissues as tumorigenic are obviously different from those of other investigators. Until differences between Reuber's criteria and those of others is resolved it will be difficult to draw conclusions from his findings.

In a study with mice (Witherup et al., 1970), males and females of the C57B1/6J and C3D2F1/J strains ingested Purina mouse chow admixed with endrin dissolved in 95% ethanol to give concentrations of 0, 0.3 or 3.0 ppm in the diet. For both strains, 100 males and 100 females constituted each treatment group and two control groups. Tissues analyzed histopathologically were the following: heart, lungs, liver, spleen, kidneys, GI tract, lymph nodes, urinary bladder, gonads, pancreas, thyroid, thymus, adrenals, brain, pituitary, spinal cord, eyes, bone marrow, nasal passages, skin and peripheral blood smears. In this lifetime study (up to 119 weeks) the overall

TABLE V-14

Number of Osborne-Mendel Female Rats with Benign Tumors[a]

Dose (ppm endrin in the diet)	Number Examined	Endocrine	Pituitary	Adrenal	Reproductive System	Liver	Total[b]
0 matched	10	4 (40%)	1 (10%)	2 (20%)	0	0	3 (30%)
Pooled	49	14 (30%)	6 (12%)	3 (6%)	4 (8%)	1 (2%)	14 (29%)
2.78	46	6 (13%)	3 (7%)	8 (18%)	9 (20%)	9 (20%)	2 (4%)
5.56	46	10 (22%)	7 (15%)	13 (28%)	3 (7%)	14 (30%)	5 (11%)
Low + high dose	92	16 (17%)	10 (11%)	21 (23%)	12 (13%)	23 (25%)	7 (8%)

[a] Sources: NCI, 1979; Reuber, 1979

[b] Total number of animals bearing benign tumors

TABLE V-15

Number of Osborne-Mendel Male Rats Ingesting Endrin with Benign Tumors[a]

Dose (ppm endrin in the diet)	Number Examined	Endocrine[b]	Pituitary[b]	Adrenal[b]	Liver[c]	Total[d]
0 matched	10	2 (20%)[e]	1 (10%)	2 (20%)	1 (10%)	5 (50%)
Pooled	49	14 (49%)	8 (16%)	3 (6%)	4 (8%)	17 (49%)
2.5	45	19 (49%)	5 (11%)	12 (27%)	13 (29%)	10 (22%)
5	45	16 (36%)	10 (22%)	3 (11%)	6 (13%)	9 (20%)
Low + high dose	90	35 (39%)	15 (17%)	15 (17%)	19 (21%)	19 (21%)

[a] Sources: NCI, 1979; Reuber, 1979

[b] Adenomas

[c] Hyperplastic nodules

[d] Total number of animals bearing benign tumors

[e] Statistical analysis (one-sided t test) revealed no statistical significance for any experimental group compared with controls

incidence of neoplasms found in each strain and diet group was not influenced by the content of endrin in the daily diet. The authors concluded that when endrin was added to the daily diet of C57Bl/6J inbred mice and C3D2F1/J hybrid mice in the amounts of 3.0 and 0.3 ppm, the pesticide was not carcinogenic to the animals. Reuber in his independent analysis of the slides of this study came to the opposite conclusion for the 0.3 ppm dose (Reuber, 1979).

In an NCI study (1979), female B6C3F$_1$ mice 35 days of age ingested endrin admixed with the diet for 80 weeks at concentrations of 0, 2.5 or 5.0 ppm and 0, 1.81 or 3.10 ppm for males. All surviving mice were killed at 90 or 91 weeks. Each treated group contained 50 animals and each control group 10 animals. In male mice, two or more animals per treated group had hepatocellular carcinoma (16% at the high dose) compared with one (10%) in the control group. A corresponding number of mice with malignancies was not observed in females. Significant incidences for any site in either sex were not observed. Because of the high mortality in the treated groups, histological examination was limited to only one section of the liver and since the numbers of control animals were only 10, an independent reviewer stated (Reuber, 1979) that no conclusions could be reached from this study.

The data (see Table V-9) are consistent with mild carcinogenic signs for endrin in Reuber's (1978) study with Osborne-Mendel rats and for C3D2F1/J mice (Witherup et al., 1970) if Reuber's reassignment of "hepatomas" to "carcinomas and sarcomas" is correct, and a borderline carcinogenicity exists in the NCI (1979) data for Osborne-Mendel rats. No malignancies were observed in rats (Treon et al., 1955; Nelson et al., 1956) or C75Bl/6J mice (Witherup et al., 1970).

Later studies suggested that endrin or its rapidly-produced metabolites might act as promoters, although some have produced conflicting evidence. Ito et al. (1980) showed that endrin (25 ppm in diet) promotes the development of preneoplastic changes in rat liver after initiation with N-nitrosodiethylamine or N-2-fluorenylacetamide. Maslansky and Williams (1981) showed that endrin (10^{-3} to 10^{-4} M) was not genotoxic in the hepatocyte primary culture (HPC)/DNA repair assay utilizing hepatocytes from male Fischer F344 rats, male CD-1 mice and male Syrian hamsters. DNA repair was observed in response to a positive control in all three systems. Thus, the mechanism of the weak hepatocarcinogenicity of endrin may reflect an epigenetic mechanism, probably involving a promotional rather than a genotoxic effect. Kurata et al. (1982) demonstrated that endrin above 5 mg/ℓ in the HGPRT system using wild-type 6-thioguanine-sensitive V79 Chinese hamster cells and mutant 6-thioguanine-resistant cells inhibited metabolic cooperation (reciprocal exchange of material between cells in contact), as do recognized tumor promoters. A concentration of 20 mg endrin/ℓ caused 80% inhibition whereas 10 mg endrin/ℓ elicited ~25% inhibition. On the other hand, Miller et al. (1981), in an abstract, reported that endrin (0-40 μM) did not change the frequency of transformation of C3H 10T1/2 cells by 3-methylcholanthrene or benzo(a)pyrene (0-10 mg/ℓ) after a 3-hour incubation.

The experiments reported here should be repeated with 12-ketoendrin as well as the syn- and anti-12-hydroxyendrins since endrin in mammals appears to be rapidly metabolized to these compounds, and endrin itself may not be the compound actually causing the observed changes.

The above studies appear to suggest that endrin, if it is a carcinogen, is a weak or borderline one, and that the observed weak effects may reflect its role as a promoter rather than as an initiator, although the crucial experiments to prove this assertion have not been performed.

Summary

The acute oral LD_{50} of endrin given to mammals by oral gavage ranged from 2.3 mg/kg to 43.4 mg/kg bw (see Table V-1). The LD_{50} following dermal exposures ranged from 10.9-92 mg/kg bw and was vehicle-dependent. A lone inhalation study indicated that 130 seven-hour exposures to 0.36 ppm endrin "vapor" were not fatal to rats, hamsters and guinea pigs; however, two of four rabbits died after 188 exposures and one of three mice died after 107 exposures (see Table V-5). Young animals appeared to be more sensitive to dietary endrin than older animals (see Table V-3). Metabolites of endrin were more acutely toxic in rats than the parent compound (see Table V-2), with 12-ketoendrin being the most toxic in both male and female rats and having acute oral LD_{50}s of 1.1 and 0.8 mg/kg bw, respectively. The acute oral LD_{50} values for endrin itself were 5.6 and 5.3 mg/kg bw, respectively, in this same study. Concentrations of endrin and 12-ketoendrin in brain tissue were reliable indicators of lethal doses in rats (see Table V-4); but in birds, 12-ketoendrin was not detected in brain tissue and endrin alone at concentratons >0.6-0.8 mg endrin/kg ww was the most reliable indicator of a lethal dose.

In chronic studies Treon et al. (1955) concluded that 1 ppm endrin in the feed was a no-effect level with respect to toxic effects in rats and dogs. In contrast, Reuber (1978) concluded that 0.1 ppm diet induced excess malignancies in rats. A conclusion of the NCI (1979) study was that endrin in the diet (2.5 and 5.0 ppm) was not carcinogenic in rats or mice although the number of matched controls was unacceptably small (20 controls vs. 100 experimental animals per dose).

Endrin was not mutagenic in microbial systems with or without microsomal activation. The insecticide proved to be teratogenic in mice and hamsters but not in rats when given by gavage in high concentrations (see Tables V-8 and V-9). Endrin acted as a behavioral teratogen in all these species. As observed with other chlorinated insecticides, endrin was more toxic to the reproductive process in birds than in mammals.

At high concentrations, $\geq$2 mg endrin/kg feed, the major effects on rats, Swiss mice and deer mice were maternal mortality, increased resorptions, and significant decrease in survival of offspring at 21 days after birth. In one study, endrin administered by oral gavage to hamsters (5 mg/kg bw/day) induced a statistically significant increase in fused ribs and cleft palate if given during the period of organogenesis. These teratogenic effects were also observed in a later study (see Table V-8). Rats and mice appeared to be less sensitive to the insecticide than hamsters. Reduced fetal weight was a frequent observation after the administration of 1 mg endrin/kg/day during gestation. In hamsters, 1.5 mg/kg/day (days 5-14 of gestation) increased locomotor activity in offspring. In rats, concentrations of 0.15-0.3 mg/kg bw/day, 7th day of pregnancy through the 15th day of lactation, did not kill dams or affect pup survival or growth; however, the offspring were 30% more active than nontreated animals. The NOEL in rats, in relation to maternal weight gain and behavioral activity appeared to be ~0.075 mg/kg bw/day. Endrin and its toxic metabolite, 12-ketoendrin, were both found in the fetus.

VI. HEALTH EFFECTS ON HUMANS

Acute Toxicity

In September 1978, the U.S. Department of Health and Human Services issued an occupational health guideline for endrin (U.S. DHHS, 1978). Symptoms of overexposure were described as follows:

> Exposure to endrin may cause sudden convulsions which may occur from 30 minutes to 10 hours after exposure. Headache, dizziness, sleepiness, weakness and loss of appetite may be present for 2-4 weeks following this exposure. A number of deaths have occurred from swallowing endrin. In less severe cases of endrin poisoning, the complaints include headache, dizziness, abdominal discomfort, nausea, vomiting, insomnia, agitation and mental confusion.
>
> Electroencephalograms may show dysrhythmic changes which frequently precede convulsions; withdrawal from exposure usually results in a normal electroencephalogram within 1-6 months. In most cases, recovery is rapid, but headache, dizziness, lethargy, weakness and anorexia may persist for 2-4 weeks.

Accidental and Intentional Poisonings. Several incidents of endrin poisoning from contaminated flour have been reported in the literature. In Wales, bread made from flour contaminated with endrin during shipment in a railway car resulted in 59 poisoning cases with no deaths in 1956. The bread contained up to 150 mg endrin/kg bread and the smallest acute dosage to elicit serious effects was calculated to be 0.2 mg/kg bw (Davies and Lewis, 1956).

In 1967, explosive outbreaks of acute endrin poisoning occurred in Doha, Qatar and Hofuf in Saudia Arabia as a result of the ingestion of food prepared with endrin-contaminated flour (Weeks, 1967; Curley et al., 1970). Twenty-six persons died and 874 were hospitalized. Many others were probably poisoned to a lesser degree but did not seek medical aid. The concentration of endrin in bread eaten by patients ranged from 48-1807 mg/kg bread. Flour used to made the bread contained 2153-3367 mg endrin/kg flour. Coble et al. (1967) reported acute endrin poisoning with sudden convulsions in three Egyptians, following ingestion of bread made with contaminated flour. In these cases, recovery was spontaneous.

Cases of fatal endrin poisoning have been reported from intentional ingestion and accidental ingestion. Tewari and Sharma (1978) reported 11 fatal poisonings; the time periods from administration of the pesticide (route not known in seven cases) to death ranged from 1-6 hours. Endrin ingestion with milk or alcohol appeared to increase toxicity as death occurred within an hour or two. Increased toxicity was attributed by the authors to more rapid absorption through the GI tract.

A pediatric hospital in Mexico reported endrin intoxication in 33 patients ranging in age from 1-16 years (Montoya Cabrera et al., 1982). Accidental ingestion accounted for 22 cases, 7 were suicides and 4 were attributed to criminal intent. The accidental poisonings resulted from the uncontrolled use of endrin in the home as a rodenticide.

A 19-year-old male who attempted suicide by ingestion of endrin developed severe pulmonary edema as well as CNS involvement. Pulmonary edema was thought to be due to chemical pneumonitis and aspiration pneumonia. The authors believed that the use of PEEP (positive end-expiratory pressure) up to 28 cm H_2O in treatment of the pulmonary edema contributed to the patient's complete recovery (Jedeikin et al., 1979).

Effects of Occupational Exposures. No illnesses were noted in seasonal workers dusting potatoes with 1% endrin dust at a calculated dermal exposure of 2.0 mg/kg bw/day in combination with a calculated respiratory exposure of 0.044 mg/kg bw/day (Wolfe et al., 1963). Also, no illnesses were noted when endrin was applied at 544-634 kg/acre as an emulsifiable concentrate for mice control at a calculated dermal dose of 0.28 mg/kg/day in combination with a calculated respiratory exposure of 0.0011 mg/kg bw/day (Wolfe et al., 1963).

Immunology. Thirteen pesticides including endrin were tested for their *in vitro* effects on human lymphocyte mitogenic responses to phytohemaglutinin and neutrophil chemotaxis (Lee et al., 1979; Park and Lee, 1980). This study was undertaken in an effort to clarify the immunosuppressive effects of many pesticides. Endrin inhibited the lymphocyte response in whole blood 11.5% and 14.2% in mononuclear cells. Neutrophil chemotaxis was inhibited 27% (77±4 vs. 105±10 cells per high power field in control cultures). In each case, inhibition was not reported to be statistically significant. All pesticides tested inhibited lymphocyte responses to some degree, and the authors suggested that the immunosuppressive effect of pesticides could be a direct effect of those chemicals on leukocytes.

Epidemiological Studies. Jager (1970c) reported an epidemiological study conducted on 826 male workers at the insecticide plant of Shell Nederland Chemie located at Pernis, Netherlands. A unit for the production of endrin was begun in February 1957. During the first 2 years of plant operation seven cases of endrin intoxication had occurred and were accompanied by convulsive seizures. All were due to acute overexposure either following an accident or to obvious neglect of precautions. Normal recovery was rapid, usually within 1-3 days.

Concentrations of endrin in the blood of 45 operators from the endrin plant were determined at least once a year from 1964-1968. The threshold level of endrin in the blood below which no sign or symptoms of intoxication were seen was 0.050-0.100 μg/mℓ. The half-life of endrin in the blood, and thus in the body, was estimated to be ~24 hours. Medical files and routine medical examinations revealed no abnormalities other than those that would be expected in any group of 233 long-term workers (4-13.3 years exposure). Results of determination of alkaline phosphatase, SGOT, SGPT, LDH, total serum proteins, and the spectra of serum proteins did not show any changes that could be correlated with the influence of the degree or duration of exposure to these insecticides on these parameters. In all cases of intoxication characterized by typical EEG changes, EEG patterns returned to normal. In the study of the parameters of enzyme induction, the data showed that occupational exposure in endrin manufacturing may cause enzyme induction in hydroxylating enzyme systems although this response appeared not to affect the health of the workers. It was not known whether endrin or its manufacturing precursors were the causative agents (Jager, 1970c).

Hoogendam et al. (1962, 1965) conducted a parallel study at the same plant. Of the 122 men exposed to all pesticides at the plant, 25 workers had EEG abnormalities (Hoogendam et al., 1962). A worker was accidentally covered with a 50% isodrin solution in xylene. He experienced dizziness and headache and profusely perspired 2 hours later. This worker suffered a typical epileptiform convulsion 6 hours after the exposure, regained consciousness within 10 minutes and rapidly recovered. There is some evidence to suggest that isodrin was partially converted to endrin in the liver of this patient (Brooks, 1969). The EEGs of patients with endrin intoxication showed paroxysms of predominantly bilateral synchronous theta-waves. In the other report (Hoogendam et al., 1965) three endrin workers suffered convulsive intoxications, two being examined for recovery of abnormal EEGs. One was exposed for 1.5 years and the other for 3 years. One recovered in 1 month, and the other in <6 months. The authors suggested that the prevailing exposure in the manufacture of aldrin, dieldrin and endrin did not disturb liver function since the levels of SGOT and SGPT returned to normal in the four workers who initially showed increases.

Ottevanger and Van Sittert (1979) continued the enzyme induction studies of Jager (1970c) on 29 endrin workers at the endrin manufacturing plant in Pernis. The D-glucaric acid concentration in urine was considered to be a useful test for enzyme induction. After 7 days of exposure, levels of the metabolite, anti-12-hydroxyendrin, increased (up to 0.360 mg/g creatinine) accompanied by a sharp rise in D-glucaric acid levels. After the long weekend, the anti-12-hydroxyendrin levels decreased, but D-glucaric acid levels remained above normal. The normal values obtained after a 6-week shutdown and maintenance period indicated that enzyme induction in endrin workers is reversible. A urinary anti-12-hydroxyendrin level of 0.130 mg/g creatinine was considered the threshold level below which enzyme induction does not occur, although exceptions were noted.

Vrij-Standhardt et al. (1979) examined urinary excretion of D-glucaric acid and total porphyrin in endrin workers. The excretion of D-glucaric acid after working was significantly increased compared with excretion after a long weekend and with a control group. The results indicated that D-glucaric acid was a useful test for exposure to endrin, but porphyrin excretion was not.

An epidemiological study was made of 216 patients with contact dermatitis in rural regions of Japan from 1968-1970 (Matsushita et al., 1980). All participants except three were farmers. Exposure occurred mainly from spraying operations. Chlorinated hydrocarbons (BHC and endrin) were thought to be responsible for 9.7% of the cases. Inadequate protection of the spray personnel, poor health conditions and carelessness were largely responsible for the dermatitis.

Wang and Grufferman (1981) performed a case control study of the association between fatal aplastic anemia and occupations entailing pesticide exposure. They found no correlation between use of chlorinated hydrocarbon pesticides, including endrin, and aplastic anemia mortality in the United States from 1950 through 1975.

Ditraglia et al. (1981) conducted a retrospective cohort study to examine the mortality of workers employed in the manufacture of chlordane, heptachlor, DDT and aldrin/dieldrin/endrin. The four plants selected for study are described in Table VI-1. Workers selected for the study had been employed at least 6 months; the personnel in contact with endrin were located at plants 2 and 3, and numbered 305 and 1155, respectively.

TABLE VI-1

Description of Plants Included in the Study of Manufacturers of Organochlorine (OC) Pesticides*

	Plant 1	Plant 2	Plant 3	Plant 4
Starting date for OC pesticide production	1946	1951	1946	1947
OC pesticides produced	Chlordane	Heptachlor, endrin	Aldrin, dieldrin, endrin	Dichloro-diphenyl-tri-chloroethane (DDT)
Other pesticides produced	None	None	Organo-bromines; organo-phosphates	None
Other chemicals at plant	Chlorine, dicyclo-pentadiene	Chlorine, chlorendic anhydride, hexachloro-cyclopenta-diene, vinyl chloride	Numerous precursors	Tri-chloro-acetaldehyde, sulfuric acid, monochloro-benzene
Location	Illinois	Tennessee	Colorado	California

*Source: Ditraglia et al., 1981

The only major category where observed deaths were greater than expected was "nonmalignant respiratory system disease" at Plant 3 (22 observed vs. 10.4 expected: SMR=212) and for "other respiratory diseases" (11 observed vs. 5.2 expected: SMR=213, $p \leq 0.05$). No statistically significant excesses or deficits in mortality for any specific cancer site were noted. In Plant 3 there was a slight excess of cancer of the esophagus (2 observed vs. 0.85 expected), cancer of the rectum (3 observed vs. 1.24 expected), cancer of the liver (2 observed. vs. 0.57 expected), and cancer of the lymphatic and hematopoietic system (6 observed vs. 4.09 expected). There was a deficit for respiratory cancer (7 observed vs. 12.64 expected) at Plant 3. Additional analyses are necessary to determine if an excess in nonmalignant respiratory disease observed at Plant 3 was associated with specific occupational exposure. Since malignant respiratory disease was not reported at Plant 2, which also manufactured endrin, endrin alone probably did not induce the lethal respiratory disease reported at Plant 3 unless exposures were much higher than those at Plant 2. However, Ditraglia et al. (1981) did not report exposure data.

Summary

Exposure to endrin is reported to cause CNS effects, convulsions and death. In less severe poisoning, recovery is usually rapid and there are no permanent effects.

A number of cases of acute poisoning resulting from accidental or intentional ingestion of endrin have been reported. The approximate oral dose producing convulsions is between 0.2 and 0.25 mg/kg bw.

No potential hazard existed during typical dermal or respiratory exposures encountered by seasonal agricultural workers exposed to endrin through dusting and spraying operations.

No fatalities or permanent abnormalities were recorded in an epidemiological study of 7233 workers engaged in the manufacture of chlorinated hydrocarbon insecticides including endrin for more than 4 years. Convulsions and CNS effects were observed in some workers. Occupational exposure in endrin manufacturing may cause enzyme induction in hydroxylating enzyme systems, but this response appeared to be reversible and to have no effect on the health of workers. Anti-hydroxyendrin levels excreted in the urine of endrin-exposed workers were correlated with excretion of D-glucaric acid.

No correlation was found between mortality from aplastic anemia and the use of chlorinated pesticides including endrin in the United States from 1950 through 1975, although no exposure data were provided to allow assessment of the importance of endrin in this study.

A mortality study of workers engaged in the manufacture of organochlorine pesticides did not identify a specific cancer risk but further studies were recommended.

VII. MECHANISMS OF TOXICITY

Acute Toxicity

The order of acute oral toxicity to endrin in various adult male species is monkey > rabbit > pheasant = quail > chicken = cattle = dog > hamster > guinea pig = rat. Young animals and female animals are more susceptible than adult males, at least in rats (Treon and Cleveland, 1955). Endrin and its metabolites are quickly eliminated except at grossly high doses, and the total half life varies between 1 and 4 days (see Chapter IV). Doses of >0.2 mg endrin/kg bw can cause convulsions (Jager, 1970d); lethality to humans may occur at doses >6 g/person (Reddy et al., 1966).

The unsubstituted methylene group in endrin is rapidly attacked to produce mostly anti- and some syn-12-hydroxyendrin, the former being eliminated as the sulfate in the urine of rabbits, female rats and hens, as the aglycone in the feces of male rats, as the glucuronide in the urine and the feces of humans, and as the free metabolite in the urine of the cow (see Chapter IV). The syn-alcohol is quickly transformed to 12-ketoendrin, which is the most acutely toxic to rats of all endrin derivatives including endrin itself (Bedford et al., 1975a). In fact, associations between lethality and the presence of 12-ketoendrin residues in the brain have been made for rats (Hutson et al., 1975), rat fetuses (Kavlock et al., 1981) and hamster fetuses (Chernoff et al., 1979) but not for birds (Stickel et al., 1979a,b); 12-ketoendrin has been postulated as the ultimate toxicant, at least in rats (Bedford et al., 1975a), hamster fetuses (Chernoff et al., 1979) and rat fetuses (Kavlock et al., 1981). The ketone is known to penetrate the blood-brain barrier, and probably the placental barrier in rats and hamsters.

Endrin is known to be a teratogen in the hamster (Chernoff et al., 1979; Gray et al., 1981) and in the mouse using a dose of 2.5 mg/kg on day 9 of gestation by oral gavage (Ottolenghi et al., 1974). Kavlock et al. (1981), however, did not confirm this conclusion for the mouse after intragastric doses of 0.5, 1.0, 1.5 and 2.0 mg/kg/day during organogenesis. Endrin crosses the placenta of the hamster and rat (Chernoff et al., 1979; Kavlock et al., 1981) and the mouse (Ottolenghi et al., 1974).

The mechanism of acute toxicity of endrin resulting in pulmonary edema and profound disturbance of the CNS remains obscure but appears to be associated with the presence of 12-ketoendrin, or the appearance of endrin residues in fatty tissues. The CNS is the major target system for acutely administered endrin. There are indications that the occurrence of convulsions is related to blood-brain barrier permeability changes (Speck and Maaske, 1958). Emerson et al. (1964) postulated that the effect was directly on the CNS and that effects caused by cerebral hemodynamics in dogs were secondary. Convulsions in dogs can be prevented by administration of succinylcholine. Walsh and Fink (1972) suggested an association with effects on plasma membrane ATPases (condition and transmission) and mitochondrial ATPases (oxidative phosphorylation) in the rat brain. Mehrotra et al. (1982) found that the influence of endrin on oxidative phosphorylation could not solely account for endrin toxicity, since inhibition of the oligomycin-sensitive Mg^{2+}-ATPase activity was not consistent, e.g., inhibition for in vitro oligomycin-sensitive beef heart and rat brain mitochondrial ATPase activity; no change for rat brain synaptosomal NA^+K^+-ATPase; no effect on oligomycin-insensitive Mg^{2+}-ATPase activity in rat brain synaptosomes and beef heart mitochondria. In fact, the work of Speck and Maaske (1958) was consistent with chronic effects on the CNS being concerned with peripheral mechanisms rather than with mechanisms in the brain itself, at least in rats. This is probably so for acute effects since succinylcholine can prevent convulsions in experimental animals (Emerson et al., 1964; Reins et al., 1966).

There are also indications that the concentrations of cytochrome P-450 in endrin-resistant animals may be greater than in susceptible species (Hartgrove et al., 1977). The effect of endrin on concentrations of cytochrome P-450 is also species-dependent, being unchanged for pine voles and increased in white mice (Hartgrove et al., 1977). Gender susceptibility may also be related to cytochrome P-450 with levels being decreased in female guinea pigs but not males; little other data are presently available (Pawar and Kachole, 1978). The concentrations of cytochrome P-450 may determine the efficiency of the conversion of endrin to its postulated ultimate toxicant, 12-ketoendrin, or the likelihood of deposition of endrin in tissues. The role of lipid peroxidation is unclear, though endrin treatment does cause a gross increase in renal and hepatic microsomal preparations from female guinea pigs (Pawar and Kachole, 1978). Endrin mode of action may also be mediated through effects on membrane permeability since hemolysis has been observed for postendrin hematocrits in dogs (Emerson et al., 1964), and since "hemorrhagic enteritis" has been noted in rats and birds (Stickel et al., 1979b).

Subchronic studies in human workers are consistent with a reversible induction of liver microsomal activity, as denoted by urinary levels of D-glucaric acid, which is dependent on the level of cytochrome P-450 (Ottevanger and Van Sittert, 1979). D-glucaric acid was not detected in urine when *anti*-12-hydroxyendrin urine levels were <0.13 mg/g of creatinine.

In rats (Treon et al., 1955), the only long-term degenerative changes in the organs from fatally-poisoned animals studied occurred in the liver and kidneys. The mechanisms responsible for such changes are not known.

Endrin is a behavioral teratogen in CD rats and Syrian Golden hamsters (Gray et al., 1981), but morphological teratogenesis occurs only in the hamster. Presumably, such effects are related to the effects on the CNS.

Thus, the mechanism of toxicity in all species appears to be associated when endrin itself or 12-ketoendrin begins to appear in tissues, mostly fatty tissues. The evolution of 12-ketoendrin does not explain the effects of endrin in birds. When the endrin source is removed, fat residues of endrin in humans and animals decrease slowly without sequelae. This indicates that a definite threshold value for expression of the acute and subchronic toxic effects of endrin is likely, probably based on endrin itself rather than 12-ketoendrin, a value which is species-dependent because of the various efficiencies and products of the metabolic processes involved.

One National Cancer Insitutute (NCI) bioassay indicated that endrin was not carcinogenic for $B6C3F_1$ mice and rats (NCI, 1979). Reuber (1979) disputed the validity of many of the conclusions of the these studies in his review and concluded that endrin was carcinogenic. Reuber (1978) also experimentally found malignant tumors in Osborne-Mendel rats. The evidence appears to indicate that endrin may be a borderline carcinogen and is more likely to be acting as an epigenetic promoter based on its nongenotoxicity (Maslansky and Williams, 1981), its promotion of the development of preneoplastic changes in rat liver (Ito et al., 1980), and its inhibition of metabolic cooperation between continuous cells (Kurata et al., 1982). Since endrin is not a direct-acting mutagen (see Section on Mutagenicity), this also supports the likelihood of an epigenetic mechanism to explain the conflicting results of cancer bioassays.

Clearly, cancer and promoter bioassays should also be performed with 12-ketoendrin and anti- and syn-12-hydroxyendrins to determine whether 12-ketoendrin accumulation or its efficiency of production could account for the conflicting cancer results in the various species, and to show if the metabolites are the actual intermediates responsible for the observed effects.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an acceptable daily intake (ADI) is calculated. An adjusted acceptable daily intake (AADI) and health advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (body weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking water volume in } \ell\text{/day}} = \text{mg}/\ell$$

where: NOAEL = no-observed-adverse-effect level

LOAEL = lowest-observed-adverse-effect level

Body weight = 70 kg for adult or 10 kg for child

Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children

Uncertainty/Safety Factor = 10, 100 or 1000

Utilizing these equations, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1-4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1-2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivities to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977, 1980) are typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.
- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data identifying a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines (NRC,

1977) for selection of an uncertainty factor, but must be considered, include the following: 1) the quality of the toxicology data, 2) the significance of the adverse effect, and 3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen, mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as 1) incomplete knowledge concerning the health effects of contaminants in drinking water, 2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results, and 3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Existing Guidelines, Recommendations and Standards

The U.S. EPA (1975) has set an interim standard for endrin in finished water of 0.0002 mg/ℓ. The U.S. EPA (1980a) proposed an ambient water criterion for endrin of 0.001 mg/ℓ. This value was the same as the maximum allowable concentration recommended at that time by the Public Health Service.

The World Health Organization (FAO/WHO, 1973) established as a guideline a maximum intake of 2 μg/kg/day, or 138.2 μg/day, for a 69.1 kg person. The proposed Index Alimentarius Commission's maximum residue limit in wheat is 20 μg/kg (Bailey et al., 1982).

The threshold limit value (8-hour TLV/TWA) recommended by the American Conference of Governmental Industrial Hygienists is 0.10 mg/m³ (0.10 µg/ℓ), with a short time exposure limit (15 minutes) of 0.30 mg/m³ (ACGIH, 1982). The Occupational Safety and Health Administration limits are the same, 0.10 mg/m³ (29 CFR 1910-1000).

The history of recommendations concerning endrin is provided in the Federal Register (1979). The U.S. EPA issued a notice of rebuttable presumption against registration and continued registration (RPAR) of endrin-containing products (e.g., Rid-a-Bird and Sorbikill) on July 27, 1976. It included three supportable risk presumptions -- risk of significant population reductions of nontarget organisms, acute toxicity to wildlife, and teratogenicity. After review, the Agency determined that the offsetting economic, social or environmental benefits were still not great enough. Thus, endrin use was cancelled in the following areas: on cotton in all areas east of interstate highway 35; on small grains to control all pests other than army cutworm, the pale western cutworm and grasshoppers; on apple orchards in the eastern United States to control meadow voles; on sugarcane to control the sugarcane borer; and on ornamentals. Registration for new uses of endrin was denied, as well as its use in unenclosed bird perch treatments. Limited use was allowed under specific conditions for the following: on cotton west of interstate 35; on small grains to control army cutworms and pale western cutworms; on apple orchards in the eastern United States to control the pine vole and in the western United States to control meadow voles; on sugarcane to control the sugarcane beetle; for conifer seed treatment; and use in enclosed bird perch treatments. New uses and registration of endrin under specified conditions were allowed as follows: as a tree paint in Texas; on alfalfa and clover seed crops in Colorado; and on small grains to control grasshoppers (in Montana). These determinations were originally issued on October 20, 1978 by the Agency.

In response to the endrin RPAR, the Agency determined that endrin was unlikely to pose an oncogenic risk to humans, and that the risk presumptions for acute dermal toxicity and fatalities to endangered species had been rebutted.

In the case of fish kills, signs stating "Contaminated: No Fishing" must be posted for 1 year after a fish kill, or for 6 months after lesser contamination unless endrin residues in the edible portion of fish are <0.3 ppm ww.

The bird species deemed potentially at risk were the Arctic and American peregrine falcons, bald eagles and brown pelicans. A NOEL of 1.5 mg/kg bw was accepted for teratogenicity in the hamster. The LOEL in the hamster was 5 mg/kg. However, behavioral studies using quail have indicated that either quail are very sensitive to the effects of endrin or the endpoints measured are more sensitive than those used in the past.

Noncarcinogenic Effects

Although the acute LD_{50} for endrin has been determined for a number of species, the available data for defining short-term health advisories (HAs) is more limited. Revzin (1968) reported an increase in the amplitude of the EEG and a tendency toward spiking after seven daily doses of 0.2 mg/kg bw endrin in rats. No effects were noted, however, after 1 or 2 days exposure to the same dose level. Speck and Maaske (1958) reported EEG changes and occasional convulsions after 1 week using daily oral doses of 3.5 mg/kg bw in rats. No effects were reported at the lower doses (0.8 and 1.7 mg/kg bw).

Nelson et al. (1956) exposed Sprague-Dawley rats to 1, 5, 25, 50 and 100 ppm endrin in the diet for 16 weeks. Body weights serum alkaline phosphatase, and an index of liver damage were measured weekly. Alkaline phosphatase showed a dose-dependent increase, while body weights in all groups exposed to endrin decreased in comparison with controls after 16 weeks. During the first 2 weeks of exposure alkaline phosphatase did not increase, but body weights relative to controls were depressed in all except the 1 ppm group. These results suggest a short-term NOAEL of 0.05 mg/kg bw based upon 1 ppm in the diet. The EEG effects reported by Revzin (1968) at 0.2 mg/kg bw support this figure.

NCI (1979) in a cancer range-finding study found decreases in body weight gain in rats administered 20 ppm, but not 10 ppm in the diet for 6 weeks. In the same study decreased body weight gains were also reported in mice administered 10 ppm, but not 5 ppm in the diet.

Information on subacute effects of endrin exposure is also available from a number of the teratology studies. Chernoff et al. (1979) reported marked maternal toxicity in Syrian golden hamsters at the lowest dose tested in this species (0.75 mg/kg bw/day for 10 days). Kavlock et al. (1981) reported maternal liver enlargement in CD-1 mice dosed to 0.5 mg/kg/day by gastric intubation for 11 days. In the same report decreases in maternal weight were seen in CD rats dosed with endrin by gastric intubation on days 7 through 20 of gestation at 0.3, but not 0.15 mg/kg bw. In addition, offspring were 30% more active than controls before weaning, but no changes were observed for offspring adults in groups treated with 0.3 or 0.15 but not 0.075 mg/kg/day. Except for the behavioral effects reported by Kavlock et al. (1981), reproductive or teratological effects were not generally noted at doses smaller than those resulting in maternal toxicity.

Treon et al. (1955) conducted chronic exposure studies on both rats and dogs. In the rat study 20/sex/group animals 28 days of age were exposed to concentrations of 1, 5, 25, 50 and 100 ppm endrin in the diet. Liver-to-body weight ratios were increased in male rats in the 5 and 25 ppm groups after 2 years of exposure. Diffuse degeneration of the brain, liver, kidneys and adrenals were reported in animals that died during exposure to concentrations of 25 ppm or greater. The average length of survival was significantly decreased in females exposed to 25 ppm or greater and in males exposed to 50 ppm or greater. Based upon liver weight change, the NOAEL is determined to be 1 ppm (0.05 mg/kg bw assuming daily food intake is equal to 5% of body weight).

In the dog study, beagles were exposed for periods of up to 18.7 months to 1, 3 or 4 ppm endrin in the diet. Based upon measured food intake the daily dose varied from 0.045-0.12 mg/kg bw for the 1 ppm group, 0.12-0.25 mg/kg bw for the 3 ppm group and 0.15-0.21 mg/kg bw for the 4 ppm group. Body weight gains were depressed in the 4 ppm but not in the 1 or 3 ppm groups. The weights of the kidneys and heart were significantly enlarged in the 3 ppm but not in the 1 ppm group. Based upon increases in kidney and heart weights the NOAEL for subchronic exposure of dogs to endrin is determined to be 0.045 mg/kg bw/day.

While other chronic studies have been conducted with the primary intent of evaluating carcinogenic response, some toxicity data have also been reported. Deichmann et al. (1970) administered endrin to rats at concentrations of 2, 6 and 12 ppm in the diet for up to 37 months. A moderate increase in centrilobular cloudy swelling of the liver along with a moderate increase in the incidence of congestive and focal hemorrhage was reported. Since the authors stated that the effects were not dose-related, it is assumed they occurred at the 2 ppm level as well as the higher doses.

In an NCI (1979) study both mice and rats were chronically exposed to endrin. The mice were administered a time-weighted-average (TWA) concentration in the diet of 1.6 and 3.2 ppm, while the rats received 3 and 6 ppm. Neither mortality nor body weights were affected by either dose. However, a variety of clinical signs usually associated with aging were observed earlier in the exposed mice and rats. Although a NOAEL was not observed in the Deichmann et al. (1970) or the NCI (1979) studies, the results of these investigations provide strong support for a NOAEL no greater than 0.05 mg/kg bw in rats and 0.13 mg/kg bw in mice (1 ppm in the diet).

Only one chronic nonmammalian study has been conducted to date. Kreitzer (1980) measured behavioral effects of endrin in adult bobwhite quail (Colinus virginianus) using nonspatial discrimination reversal tasks. The birds were fed 0.1 and 1.0 ppm endrin in the diet (0.01 and 0.10 mg/kg bw if it is assumed the birds eat an amount equivalent to 10% of bw/day) for up to 240 days. Significantly increased error rates were detected at both levels of exposure.

While the results of this study indicate that the NOEL should be lower than values determined from other chronic studies, it is uncertain how they relate to those of mammalian exposures. Acute LD_{50} studies on pigeons (Revzin, 1966) suggest that some species of birds may be more sensitive to endrin exposure than mammals. It is also uncertain whether the behavioral effects can be definitely classified as detrimental. For example, if exposure reduces the desire to achieve the reward for correct performance, accuracy may decline even though the ability to perform accurately does not.

Quantification of Toxicological Effects

Derivation of 1-Day HAs. Revzin (1968) reported alterations in the EEG of squirrel monkeys after 7 daily doses of 0.2 mg/kg endrin. No effects were noted, however, at this dose level for shorter exposures. Thus, 0.2 mg/kg can be considered a NOAEL for a 1-day exposure. If this study is considered suitable for the development of a 1-day HA, it can be derived thus:

$$\text{1-day HA adult} = \frac{0.2 \text{ mg/kg bw/day} \times 70 \text{ kg}}{100 \times 2 \text{ ℓ/day}} = 0.070 \text{ mg/ℓ}$$

$$\text{1-day HA child} = \frac{0.2 \text{ mg/kg bw/day} \times 10 \text{ kg}}{100 \times 1 \text{ ℓ/day}} = 0.020 \text{ mg/ℓ}$$

where:

0.2 mg/kg/day = no-effect level for EEG changes in squirrel monkeys after 1-day exposure
70 kg = weight of a human adult
10 kg = weight of a human child

2 ℓ/day = daily adult water consumption

1 ℓ/day = daily child water consumption

100 = uncertainty factor based on an acceptable short-term animal exposure study identifying a NOAEL. This represents two 10-fold decreases in dose for both intra- and interspecies variability to the toxicity of endrin since specific information is not available.

Based upon data from Davies and Lewis (1956) in which the human response to ingestion of bread contaminated with 150 ppm endrin was reported, Hayes (1963) estimated that the dosage necessary to produce a single convulsion in man is ~0.25 mg/kg. If this estimate is considered suitable for the development of a 1-day HA, it can be derived thus:

$$\text{1-day HA adult} = \frac{0.25 \text{ mg/kg bw/day} \times 70 \text{ kg}}{100 \times 2 \ \ell\text{/day}} = 0.088 \text{ mg/}\ell$$

$$\text{1-day HA child} = \frac{0.25 \text{ mg/kg bw/day} \times 10 \text{ kg}}{100 \times 1 \ \ell\text{/day}} = 0.025 \text{ mg/}\ell$$

where:

0.25 mg/kg/day = minimum-effect level for convulsions in humans

70 kg = weight of a human adult

10 kg = weight of a human child

2 ℓ/day = daily adult water consumption

1 ℓ/day = daily child water consumption

100 = uncertainty factor, representing a 10-fold decrease in dose for interspecies variability and an additional 10-fold decrease in dose for effects at an estimated dose.

It is recommended that concentrations of 0.070 and 0.020 mg/ℓ for an adult and child, respectively be accepted as the 1-day HA for endrin. The derivations from the human data are based upon rather severe effects and dosages are estimated rather than actual measurements. The HAs based upon the Hayes (1963) estimates, however, are only slightly greater than the ones developed using the Revzin (1968) study and, thus, provides some support for the recommended values.

Derivation of 10-Day HAs. In the teratology studies by Kavlock et al. (1981) decreases in maternal weights were reported for rats dosed 14 consecutive days with 0.3 but not 0.15 mg/kg bw endrin. If this study is considered suitable for the development of a 10-day HA it can be derived thus:

$$\text{10-day HA adult} = \frac{0.15 \text{ mg/kg bw/day} \times 70 \text{ kg}}{100 \times 2 \ \ell\text{/day}} = 0.053 \text{ mg/}\ell$$

$$\text{10-day HA child} = \frac{0.15 \text{ mg/kg bw/day} \times 10 \text{ kg}}{100 \times 1 \ \ell\text{/day}} = 0.015 \text{ mg/}\ell$$

where:

0.15 mg/kg/day = the no-effect level for short-term effects in exposed animals
70 kg = weight of a human adult
10 kg = weight of a human child
2 ℓ/day = daily adult water consumption
1 ℓ/day = daily child water consumption
100 = uncertainty factor based on an acceptable short-term animal study identifying a NOAEL. This represents two 10-fold decreases in dose for both intra- and interspecies variability to the toxicity of endrin since specific information is not available.

Kavlock et al. (1981) also reported behavioral effects in offspring of rats treated for 14 consecutive days with 0.15 but not 0.075 mg/kg endrin. If these effects are considered suitable for the development of a 10-day HA, it can be derived thus:

$$\text{10-day HA adult} = \frac{0.075 \text{ mg/kg bw/day} \times 70 \text{ kg}}{100 \times 2 \ \ell\text{/day}} = 0.026 \text{ mg/}\ell$$

$$\text{10-day HA child} = \frac{0.075 \text{ mg/kg bw/day} \times 10 \text{ kg}}{100 \times 1 \ \ell\text{/day}} = 0.0075 \text{ mg/}\ell$$

where:

0.075 mg/kg/day = no-effect level for behavioral changes in offspring of exposed rats

70 kg = weight of a human adult

10 kg = weight of a human child

2 ℓ/day = daily water consumption adult

1 ℓ/day = daily water consumption child

100 = uncertainty factor based upon an acceptable short-term animal study identifying a NOAEL. This represents two 10-fold decreases in dose for both intra- and interspecies variability to the toxicity of endrin since specific information is not available.

Nelson et al. (1956) reported that body weights of rats exposed 1 or 2 weeks to 5 ppm endrin but not 1 ppm in the diet decreased relative to controls. If this study is considered suitable for the development of a 10-day HA, it can be derived thus:

$$\text{10-day HA adult} = \frac{0.05 \text{ mg/kg bw/day} \times 70 \text{ kg}}{100 \times 2 \ \ell\text{/day}} = 0.018 \text{ mg/}\ell$$

$$\text{10-day HA child} = \frac{0.05 \text{ mg/kg bw/day} \times 10 \text{ kg}}{100 \times 1 \ \ell\text{/day}} = 0.0050 \text{ mg/}\ell$$

where:

0.05 mg/kg/day = no-effect level for body weight changes based upon 1 ppm in the diet

70 kg = weight of a human adult

10 kg = weight of a human child

2 ℓ/day = daily adult water consumption

1 ℓ/day = daily child water consumption

100 = uncertainty factor based upon an acceptable short-term animal study identifying a NOAEL. This represents two 10-fold decreases in dose for both intra- and interspecies variability to the toxicity of endrin since specific information is not available.

It is recommended that the 10-day HAs developed from the results of the Nelson et al. (1956) study be accepted. Depressed body weight is considered an adequate indication of detrimental effects. Behavioral effects in offspring of rats administered similar doses provides additional support for this HA.

Derivation of Lifetime AADI

Treon et al. (1955) exposed dogs for up to 18.7 months to 1, 3 or 4 ppm endrin in the diet. Based on measured food intake the daily dose varied from 0.045-0.12 mg/kg bw for the 1 ppm group, 0.12-0.25 mg/kg bw for the 3 ppm group and 0.15-0.21 mg/kg bw for the 4 ppm group. Increases in heart and kidney weights were noted at 3 and 4 ppm but not at 1 ppm. If this study is considered suitable for the development of an ADI it can be derived thus:

$$\text{ADI} = \frac{0.045 \text{ mg/kg bw/day} \times 70 \text{ kg}}{1000} = 0.0032 \text{ mg/day}$$

where:

0.045 mg/kg bw/day = no-effect level for heart and kidney weights in dogs

70 kg = weight of an adult human

1000 = uncertainty factor for an acceptable subchronic animal study, representing two 10-fold decreases in dose for both intra- and interspecies variability to the toxicity of endrin since specific information is not available and an additional 10-fold decrease in dose since a subchronic study is being used to estimate a lifetime ADI.

Using 0.0032 mg/day as the ADI, the adjusted ADI (AADI) is derived as follows:

$$\text{AADI} = \frac{0.0032 \text{ mg/day}}{2 \text{ ℓ/day}}$$

$$= 0.0016 \text{ mg/ℓ}$$

where: 2 ℓ/day = adult water consumption

A summary of the data used to calculate the HAs and AADI is provided in Table VIII-1.

The recommended AADI (0.0016 mg/ℓ) is higher than the present interim drinking water standard of 0.0002 mg/ℓ. In the development of both the interim standard and the presently recommended AADI, a NOAEL of 1 ppm in dogs was used. For the 1975 standard the food intake equal to 2% of body weight was assumed. This resulted in a daily estimated endrin intake of 0.02 mg/kg bw. In the present case, the intake of endrin, based upon measured food intake, varied from 0.045-0.12 mg/kg bw for the 1 ppm concentration. The lower value of 0.045 was utilized in the derivation. It is felt that measured intake is preferable to estimated when available.

Carcinogenic Effects

The potential carcinogenic effect of endrin was evaluated in Carworth Farm rats (Treon et al., 1955), Osborne-Mendel rats (Deichmann et al., 1950; NCI, 1979), C57Bl/CJ mice (Witherup et al., 1970), C3D2F1/J mice (Witherup et al., 1970) and B6C3F1 mice (NCI, 1979). The results were negative in all of these studies. Treon et al. (1955) also failed to note any increase in tumorigenesis in dogs exposed up to 18.7 months at the maximum tolerated dose.

The only positive carcinogenic effects of endrin were reported by Reuber (1978, 1979). In a study using Osborne-Mendel rats administered endrin in the diet at concentrations of 0.1, 5, 20 or 25 ppm, the total number of

TABLE VIII-1

Summary of Data Used to Derive HA or AADI

Criteria	Dose (mg/kg bw/day)	Duration	Effect	Value of HA or AADI		Reference
				Child (mg/ℓ)	Adult (mg/ℓ)	
1-Day HA[a]	0.2	1 day	NOAEL: EEG changes in squirrel monkeys	0.02	0.07	Revzin, 1968
1-Day HA	0.25	single exposure	convulsions in humans	0.025	0.088	Davies and Lewis, 1956
10-Day HA	0.15	14 days	NOAEL: decreases in maternal weights in rats	0.015	0.053	Kavlock et al., 1981
10-Day HA	0.075	14 days	NOAEL: behavioral changes in offspring of exposed rats	0.0075	0.026	Kavlock et al., 1981
10-Day HA[a]	0.05	1-2 weeks	NOAEL: body weight changes of rats	0.005	0.018	Nelson et al., 1956
Lifetime AADI[a]	0.045	up to 18.7 months	NOAEL: heart and kidney weight in dogs	b/	0.0016	Treon et al., 1955

[a] Recommended criteria

[b] Not calculated because a child will not remain in the high risk population for a lifetime.

malignant tumors was increased in all exposed groups (see Table V-10) (Reuber, 1978). No more than 2 tumors/group, however, were reported for any one site. Moreover, no dose response was apparent, with the greatest number of tumors occurring in the 0.1 ppm group. This, however, could be caused by toxicity factors at the higher doses. Reuber (1979) also re-evaluated tissue sections from the NCI (1979) and Witherup et al. (1970) studies. In his re-evaluation he concluded that the NCI rat study and the Witherup mouse study were positive for cancer induction, while results of the NCI mouse study were inconclusive. Unless evidence is presented to indicate why the NCI (1979) and the Witherup et al. (1970) studies were evaluated incorrectly initially, Reuber's reassessment cannot be accepted. Furthermore, since Reuber's criteria appear to differ from those of other investigators, results of his own study could be considered questionable.

There are no clinical reports available relating endrin exposure to induction of cancer in humans. Ditraglia et al. (1981) conducted a retrospective cohort study to examine the mortality of workers employed in the manufacture of chlordane, heptachlor, DDT and aldrin/dieldrin/endrin. No statistically significant excess for any specific cancer site was noted. However, since no exposure data are reported, the results of this study are inconclusive. While there is no evidence linking endrin to cancer induction in humans, the amount of data available is insufficient to allow definite conclusions to be drawn.

On the basis of results from both human and animal investigations, it is concluded that there is insufficient evidence to classify endrin as a carcinogen. Since no definite evidence for the carcinogenicity of endrin is available, no quantitation of effects was done.

Special Considerations

Endrin given to the dam at dose levels ~10-fold in excess of the chronic NOEL in adult nonpregnant animals has been associated with reduced fetal weight in hamsters and mice. At levels comparable to the chronic NOEL, endrin exposure resulted in increased locomotor activity of offspring of rats and hamsters. Thus, unborn children must be considered a potentially sensitive group.

The general public in the Missouri and Mississippi basins between March 1964 and June 1967 were exposed to endrin in drinking water (Schafer et al., 1967) and in 1976 in Ottawa, Canada (Williams et al., 1978). These situations occurred in agricultural areas. Acid drinking waters are more likely to contain endrin ketone than endrin itself (ApSimon et al., 1982), also keeping in mind that endrin cannot be analyzed well in acid water, in contrast to endrin ketone (Millar et al., 1981). Thus, people living in areas of high endrin use have more potential for risk than have the general population.

Farming communities and workers near areas of endrin application may be exposed not only to endrin (Wolfe et al., 1963, 1967; U.S. EPA, 1971, 1979; Arthur et al., 1976; Jegier, 1964), but also to the major product of sunlight degradation, the half-cage ketone identified also in environmental samples (Zabik et al., 1971). Exposure to this product may increase their risk.

Workers exposed to endrin in occupational environments have been known to suffer convulsions (Jager, 1970a,c). Such workers are the best study populations for monitoring signs of cancer. Poisoning episodes have also been reported for endrin-contaminated flour (Coble et al., 1967; Weeks, 1967; Curley et al., 1970).

Previous exposure to related compounds can increase susceptibility to the toxic effects of endrin. Pretreatment of quail with chlordane at dosages less than the NOAEL (10 ppm in the diet for 10 weeks) resulted in greater mortality in birds subsequently administered 10 ppm endrin in the diet than in those administered endrin alone (Ludke, 1976). Of the birds that died, the ones treated with endrin alone had lower brain endrin concentrations than in those pretreated with chlordane.

Radiation may increase the response to endrin. Irradiation of rats with gamma particles (900 rads) before injection of 10 mg/kg bw endrin to rats resulted in a greater increase in SGOT, SGPT, and a greater decrease in acid and alkaline phosphatase, succinic dehydrogenase and glucose-6-phosphatase than in rats treated with endrin alone (Meena et al., 1978).

Finally, stress may lower the threshold for the toxic effects of endrin. The survival times of female field mice (Peromyscus maniculatus) were shorter during combined cold and starvation, at doses of endrin as low as 1 ppm in the diet, than in stressed mice that received no endrin (Morris, 1968).

Summary

The NOAEL for acute exposure to endrin is determined to be 0.2 mg/kg bw/day based upon EEG changes in squirrel monkeys. The minimum dosage necessary to induce convulsions in humans was estimated to equal 0.25 mg/kg bw/day. Based upon the NOAEL for squirrel monkeys and supported by the minimum-effect level in humans, a 1-day HA is proposed to be 0.070 mg/ℓ for adults and 0.020 mg/ℓ for children.

The NOAEL for short-term exposure to endrin is determined to be 0.05 mg/kg bw/day based upon body weight changes in rats. Utilizing this NOAEL a 10-day HA is proposed to be 0.018 mg/ℓ for adults and 0.0050 mg/ℓ for children.

The NOAEL for subchronic exposure to endrin is determined to be 0.045 mg/kg bw/day based upon changes in heart and kidney weights in dogs. Utilizing this NOAEL a chronic AADI of 0.0016 mg/ℓ is proposed.

There is insufficient evidence to determine the carcinogenicity of endrin in either animals or humans. As a result, a quantitative risk estimate for cancer induction was not derived.

IX. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1982. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1984. Cincinnati, OH. p. 17.

Ames, B.N., J. McCann and E. Yamasaki. 1975. Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat. Res. 31: 347-364.

Anonymous. 1979. Beginning of the end for use of endrin. J. Am. Med. Assoc. 241: 353.

ApSimon, J.W., K. Yamasaki, A. Fruchier, A.S. Chau and C.P. Huber. 1982. Apparent carbon-carbon bond cleavage in an epoxide. 2,3,4,4,5,6-hexachloro-12-oxopentacyclo[5.4.1.1.^{8},^{11}.0^{3},^{10}.0^{5},^{9}]tridecane: A minor product from the acid treatment of endrin. Can. J. Chem. 60: 501-508.

Arthur, R.D., J.D. Cain and B.F. Barrentine. 1976. Atmospheric levels of pesticides in the Mississippi delta. Bull. Environ. Contam. Toxicol. 15: 129-134.

Bailey, S., G.B. Collins, F.B. Fishwick, H.V. Hart, D.F. Horler and K.A. Scudamore. 1982. Pesticide residues in foodstuffs in Great Britain: Organochlorine pesticides, organophosphorus pesticides and fumigant residues in home-produced and imported wheat. Pestic. Sci. 13: 373-378.

Baldwin, M.K. and D.H. Hutson. 1980. Analysis of human urine for a metabolite of endrin by chemical oxidation and gas-liquid chromatography as an indicator of exposure to endrin. Analyst. 105: 60-65.

Baldwin, M.K., J. Robinson and D.V. Parke. 1970. Metabolism of endrin in the rat. J. Agric. Food Chem. 18: 1117-1123.

Baldwin, M.K., J.V. Crayford, D.H. Hutson and D.L. Street. 1976. The metabolism and residues of ^{14}C-endrin in lactating cows and laying hens. Pestic. Sci. 7: 575-594.

Bedford, C.T., D.H. Hutson and I.L. Natoff. 1975a. The acute toxicity of endrin and its metabolites to rats. Toxicol. Appl. Pharmacol. 33: 115-121.

Bedford, C.T., R.K. Harrod, E.C. Hoadley and D.H. Hutson. 1975b. The metabolite fate of endrin in the rabbit. Xenobiotica. 5: 485-500.

Bedford, C.T. and D.H. Hutson. 1976. The comparative metabolism in rodents of the isomeric insecticides dieldrin and endrin. Chem. Ind. (London). (10): 440-447.

Benes, V. 1969. Mutagenic activity of some pesticides in Drosophilia melanogaster. Ind. Med. 38: 442-444.

Bird, C.W., R. Khan and A.C. Richardson. 1978. Structure of endrin aldehyde. Chem. Ind. (London). (7): 231-232.

Blus, L., E. Cromartie, L. McNease and T. Joanen. 1979. Brown pelican: Population status, reproductive success, and organochlorine residues in Louisiana, 1971-1976. Bull. Environ. Contam. Toxicol. 22: 128-134.

Blus, L.J. 1978. Short-tailed shrews: Toxicity and residue relationships of DDT, dieldrin and endrin. Arch. Environ. Contam. Toxicol. 7: 83-97.

Blus, L.J. 1982. Further interpretation of the relation of organochlorine residues in brown pelican eggs to reproductive success. Environ. Pollut. Series A. 28: 15-33.

Brooks, G.T. 1969. The metabolism of diene-organochlorine (cyclodiene) insecticides. Residue Rev. 27: 81-138.

Brooks, G.T. 1974a. Chlorinated Insecticides, Vol. 1. Technology and Applications, CRC Press, Cleveland, OH. p. 164-166.

Brooks, G.T. 1974b. Chlorinated Insecticides, Vol. 1. Technology and Applications, CRC Press, Cleveland, OH. p. 82-83.

Butler, L.C., D.C. Staiff, G.W. Sovocool, N.K. Wilson and J.A. Magnuson. 1981. Reductive degradation of dieldrin and endrin in the field using acidified zinc. J. Environ. Sci. Health. B16: 395-408.

Cabral, J.R.P., F. Raitano, T. Mollner, S. Bronczyk and P. Shubik. 1979. Acute toxicity of pesticides in hamsters. Toxicol. Appl. Pharmacol. 48: A192.

CHEMLINE Data Base for CAS Indexing Terms and CAS Registry Numbers. 1983: June.

Chernoff, N. and R.J. Kavlock. 1982. An in vivo teratology screen utilizing pregnant mice. J. Toxicol. Environ. Health. 10: 541-550.

Chernoff, N., R.J. Kavlock, R.C. Hanisch, et al. 1979. Perinatal toxicity of endrin in rodents. I. Fetotoxic effects of prenatal exposure in hamsters. Toxicology. 13: 155-165.

Coble, Y., P. Hildebrandt, J. Davis, F. Raasch and A. Curley. 1967. Acute endrin poisoning. J. Am. Med. Assoc. 202: 153-157.

Cole, J.F., L.M. Klevay and M.R. Zavon. 1970. Endrin and dieldrin: A comparison of hepatic excretion rates in the rat. Toxicol. Appl. Pharmacol. 12: 547-555.

Cox, R.H. and J.D. McKinney. 1978. Carbon-13 NMR spectra of some chlorinated polycyclodiene pesticides. Org. Magn. Reson. 11: 541-546.

Cummings, J.G., K.T. Zee, V. Turner, F. Quinn and R.E. Cook. 1966. Residues in eggs from low-level feeding of five chlorinated hydrocarbon insecticides to hens. J. Assoc. Off. Anal. Chem. 49: 354-364.

Curley, A., R.W. Jennings, H.T. Mann and V. Sedlak. 1970. Measurement of endrin following epidemics of poisoning. Bull. Environ. Contam. Toxicol. 5: 24-29.

Davies, G.M. and I. Lewis. 1956. Outbreak of food poisoning from bread made of chemically contaminated flour. Br. Med. J. 11: 393-398.

Deichmann, W.B., W.E. MacDonald, E. Blum, et al. 1970. Tumorigenicity of aldrin, dieldrin and endrin in the albino rat. Ind. Med. 39: 426-434.

Dikshith, T.S.S. and K.K. Datta. 1973. Endrin induced cytological changes in albino rats. Bull. Environ. Contam. Toxicol. 9: 65-69.

Ditraglia, D., D.P. Brown, T. Namekata and N. Iverson. 1981. Mortality study of workers employed at organochlorine pesticide manufacturing plants. Scand. J. Work Environ. Health. 7: 140-146.

Eichers, T.R. 1980. Evaluation of pesticide supplies and demand for 1980. U.S. Department of Agriculture, Economics, Statistics and Cooperatives Service. Agric. Econ. Rep. 454. p. 8-9.

Emerson, T.E., Jr., C.M. Brake and L.B. Hinshaw. 1964. Cardiovascular effects of the insecticide endrin. Can. J. Physiol. Pharmacol. 42: 41-51.

FAO/WHO (Food and Agricultural Organization/World Health Organization). 1973. 1972 evaluation of some pesticide residues in food. FAO Agric. Studies No. 90.

Feare, C.J., D.D.B. Summers and R. Longstaff. 1978. Toxicity of endrin-treated pear buds to bullfinches. Exp. Hortic. 30: 42-45.

Federal Register. 1979. Endrin intent to cancel registrations and denial of applications for registration of pesticide products containing endrin, and statement of reasons. 44: 43632-43657.

Frank, R., H.E. Braun, M. Holdrinet, G.J. Sirons, E.H. Smith and D.W. Dixon. 1979. Organochlorine insecticides and industrial pollutants in the milk supply of southern Ontario, Canada - 1977. J. Food Prot. 42: 31-37.

Gaines, T.B. 1969. Acute toxicity of pesticides. Toxicol. Appl. Pharmacol. 14: 515-534.

Goggelman, W., G. Bonse, D. Henschler and H. Creim. 1978. Mutagenicity of chlorinated cyclopentadienes due to metabolic activation. Biochem. Pharmacol. 27: 2927-2929.

Good, E.E. and G.W. Ware. 1969. Effects of insecticides on reproduction in the laboratory mouse. IV. Endrin and dieldrin. Toxicol. Appl. Pharmacol. 14: 201-203.

Grant, W.F. 1973. Cytological effects of environmental mutagens-pesticides. Mutat. Res. 21: 221-222.

Graves, J.B. and J.R. Bradley. 1965. Response of Swiss albino mice to intraperitoneal injection of endrin. J. Econ. Entomol. 58: 178-179.

Gray, L.E., Jr., R.J. Kavlock, N. Chernoff, J.A. Gray and J. McLamb. 1981. Perinatal toxicity of endrin in rodents. III. Alterations of behavioral ontogeny. Toxicology. 21: 187-202.

Green, V.A. 1969. Effects of pesticides on rat and chick embryo. In: Trace Substances in Environmental Health. III. Proc. Univ. Missouri 3rd Ann. Conf. Trace Subst. Environ. Health. p. 183-209.

Gregory, W.W. 1970. Bioaccumulation of endrin from natural food sources in the eastern bobwhite quail, Colinus virginianus virginianus L. Diss. Abstr. Int. 31: 7368-7378.

Gregory, W.W., J.K. Reed and L.G. Webb. 1972. Bioaccumulation of endrin from natural food sources in the eastern bobwhite quail, Colinus virginianus virginianus L. In: Proc. Ann. Conf. Southeast Assoc. Game Fish. 25: 156-164.

Hadler, M.R. 1982. Poisons, economic. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. Wiley-Interscience, New York. 18: 317.

Hartgrove, R.W., Jr., S.G. Hundley and R.E. Webb. 1977. Characterization of the hepatic mixed function oxidase system in endrin-resistant and -susceptible pine voles. Pestic. Biochem. Physiol. 7: 146-153.

Hayes, W.H. 1963. Clinical Handbook on Economic Poisons. U.S. Pub. Health Serv., Publ. 476. (Cited in: Coble et al., 1967)

Heinz, G.H. and R.W. Johnson. 1979. Elimination of endrin by mallard ducks. Toxicology. 12: 189-196.

Hinshaw, L.B., L.A. Solomon, D.A. Reins, V. Fiorica and T.E. Emerson. 1966. Effects of the insecticide endrin on the cardiovascular system of the dog. J. Pharmacol. Exp. Ther. 153: 225-236.

Hirom, P.C., P. Millburn, R.L. Smith and R.T. Williams. 1972. Species variations in the threshold molecular-weight factor for the biliary excretion of organic anions. Biochem. J. 129: 1071-1077.

Hoogendam, I., J.P.J. Versteeg and M. de Vlieger. 1962. Electroencephalograms in insecticide toxicity. Arch. Environ. Health. 4: 86-94.

Hoogendam, I., J.P.J. Versteeg and M. de Vlieger. 1965. Nine years' toxicity control in insecticide plants. Arch. Environ. Health. 10: 441-448.

Hudson, R.H., M.A. Haegele and R.K. Tucker. 1979. Acute oral and percutaneous toxicity of pesticides to mallards: Correlations with mammalian toxicity data. Toxicol. Appl. Pharmacol. 47: 451-460.

Hunter, C.G., A. Rosen, R.T. Williams, J.G. Reynolds and A.N. Worten. 1960. Studies on the fate of aldrin, dieldrin and endrin in the mammal. Mededcl. Landbouw. Op. Staat. Gent. 25: 1296-1307.

Hutson, D.H. 1981. The metabolism of insecticides in man. Prog. Pestic. Biochem. 1: 247-285.

Hutson, D.H. and E.C. Hoadley. 1974. The oxidation of a cyclic alcohol (12-hydroxyendrin) to a ketone (12-keto-endrin) by microsomal mono-oxygenation. Chemosphere. 3: 205-210.

Hutson, D.H., M.K. Baldwin and E.C. Hoadley. 1975. Detoxification and bioactivation of endrin in the rat. Xenobiotica. 5: 697-714.

Ito, N., M. Tatematsu, K. Nakanishi, et al. 1980. The effects of various chemicals on the development of hyperplastic liver nodules in hepatectomized rats treated with N-nitrosodiethylamine or N-2-fluorenylacetamide. Gann. 71: 832-842.

Ivie, G.W. and J.E. Casida. 1971a. Sensitized photodecomposition and photosensitizer activity of pesticide chemicals exposed to sunlight on silica gel chromatoplates. J. Agric. Food Chem. 19: 405-409.

Ivie, G.W. and J.E. Casida. 1971b. Photosensitizers for the accelerated degradation of chlorinated cyclodienes and other insecticide chemicals exposed to sunlight on bean leaves. J. Agric. Food Chem. 19: 410-416.

Jager, K.W. 1970a. Aldrin, Dieldrin, Endrin and Telodrin. Elsevier Publishing Company, New York. p. 135-136.

Jager, K.W. 1970b. Aldrin, Dieldrin, Endrin and Telodrin. Elsevier Publishing Company, New York. p. 78-83.

Jager, K.W. 1970c. Aldrin, Dieldrin, Endrin and Telodrin. Elsevier Publishing Company, New York. p. 97-224.

Jager, K.W. 1970d. Aldrin, Dieldrin, Endrin and Telodrin. Elsevier Publishing Company, New York. p. 84-87.

Jedeikin, R., R. Kaplan, A. Shapira, H. Radwan and S. Hoffman. 1979. The successful use of "high level" PEEP in near fatal endrin poisoning. Crit. Care Med. 7: 168-170.

Jegier, Z. 1964. Health hazards in insecticide spraying of crops. Arch. Environ. Health. 8: 670-674.

Kaiser, T.E., W.L. Reichel, L.N. Locke, et al. 1980. Organochlorine pesticide PCB and PBB residues and necropsy data for bald eagles from 29 states 1975-1977. Pestic. Monit. J. 13: 145-149.

Kavlock, R.J., N. Chernoff, R.C. Hanisch, J. Gray, E. Rogers and L.E. Gray, Jr. 1981. Perinatal toxicity of endrin in rodents. II. Fetotoxic effects of prenatal exposure in rats and mice. Toxicology. 21: 141-150.

Kenaga, E.E. 1980. Correlation of bioconcentration factors of chemicals in aquatic and terrestrial organisms with their physical and chemical properties. Environ. Sci. Technol. 14: 553-556.

Kiigemagi, V., R.G. Sprowls and L.C. Terriere. 1958. Endrin content of milk and body tissues of dairy cows receiving endrin daily in their diet. J. Agric. Food Chem. 6: 518-521.

Klein, W., W. Mueller and F. Korte. 1968. Excretion, distribution, and metabolism of endrin-(14C) in rats. Justus Liebigs Ann. Chem. 713: 180-185.

Korte, F. 1967. Metabolism of aldrin, dieldrin, and endrin. In: Symp. Science and Technology of Residual Insecticides in Food Production with Special Reference to Aldrin and Dieldrin. p. 102-117.

Korte, F., W. Klein, I. Weisgerber, R. Kaul, W. Mueller and A. Djirsarai. 1970. Recent results in studies on the fate of chlorinated insecticides. In: Inter-American Conf. on Toxicology and Occupational Medicine; 6th and 7th Pesticide Symp.; Collection of Papers, W.B. Deichmann, J.L. Radomski and R.A. Penalver, Ed. Halos and Associates, Coral Gables, FL. p. 51-56.

Kreitzer, J.F. 1980. Effects of toxaphene and endrin at very low dietary concentrations on discrimination acquisition and reversal in bobwhite quail, Colinus virginianus. Environ. Pollut. A23: 217-230.

Kurata, M., K. Hirose and M. Umeda. 1982. Inhibition of metabolic cooperation in Chinese hamster cells by organochlorine pesticides. Gann. 73: 217-221.

Kutz, F.W., S.C. Strassman and J.F. Sperling. 1979. Survey of selected organochlorine pesticides in the general population of the United States: Fiscal years 1970-1975. Ann. N.Y. Acad. Sci. 320: 60-68.

Lee, T.P., R. Moscati and B.H. Park. 1979. Effects of pesticides on human leukocyte functions. Res. Commun. Chem. Pathol. Pharmacol. 23: 597-609.

Long, W.H., L.D. Newsom and A.M. Mullins. 1961. Endrin residues in the fat of lambs grazed on endrin-treated pasture. J. Econ. Entomol. 54: 605-606.

Ludke, J.L. 1976. Organochlorine pesticide residues associated with mortality: Additivity of chlordane and endrin. Bull. Environ. Contam. Toxicol. 16: 253-260.

McCann, J. and B.N. Ames. 1976. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals: Discussion. Proc. Natl. Acad. Sci. U.S.A. 73: 950-954.

McCann, J.A., W. Teeters, D.J. Urban and N. Cook. 1981. A short-term dietary toxicity test on small mammals. Am. Soc. Test. Mater. Spec. Tech. Publ. 757: 132-142.

MacLeod, K.E., R.C. Hanisch and R.G. Lewis. 1982. Evaluation of gel permeation chromatography for cleanup of human adipose tissue samples for GC/MS analysis of pesticides and other chemicals. J. Anal. Toxicol. 6: 38-40.

Main, D.C. 1978. Endrin toxicity in cagebirds. Aust. Vet. J. 54: 198-199.

Mangani, F., G. Crescentini and F. Bruner. 1981. Sample enrichment for determination of chlorinated pesticides in water and soil by chromatographic extraction. Anal. Chem. 53: 1627-1632.

Marion, W.R. 1976. Organochlorine pesticide residues in plain chachalacas from south Texas, 1971-72. Pestic. Monit. J. 10: 84-86.

Maslansky, C.J. and G.M. Williams. 1981. Evidence for an epigenetic mode of action in organochlorine pesticide hepatocarcinogenicity: A lack of genotoxicity in rat, mouse, and hamster hepatocytes. J. Toxicol. Environ. Health. 8: 121-130.

Matsushita, T., S. Nomura and T. Wakatsuki. 1980. Epidemiology of contact dermatitis from pesticides in Japan. Contact Dermatitis. 6: 255-259.

Meena, K., P.K. Gupta and S.R. Bawa. 1978. Endrin-induced toxicity in normal and irradiated rats. Environ. Res. 16: 373-382.

Mehrotra, B.D., S.K. Bansal and D. Desaiah. 1982. Comparative effects of structurally related cyclodiene pesticides on ATPases. J. Appl. Toxicol. 2: 278-283.

Metcalf, R.L. 1981. Insect control technology. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley & Sons, New York. 13: 435.

Millar, J.D., R.E. Thomas and H.J. Schattenberg, III. 1981. Determination of organochlorine pesticides and polychlorinated biphenyls in water by gas chromatography. Anal. Chem. 53: 214-219.

Montoya Cabrera, M.A., M. Escartin Chavez, M. Reynoso Garcia and C.G. Strecker. 1982. Intoxicacion por endrin. Informe de 33 casos. Rev. Med. Inst. Mex Seguro Soc. (Mexico). 20: 79-84. (Spa.)

Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116: 185-216.

Morris, R.D. 1968. Effects of endrin feeding on survival and reproduction in the deer mouse, _Peromyscus_ _maniculatus_. Can. J. Zool. 46: 951-958.

Muir, C.M.C. 1968. No title provided. (Cited in: Jager, 1970b,d)

Nagelsmit, A., P.W. Van Vliet, W.A.M. Van der Wiel-Wetzels, et al. 1979. Porphyrins as possible parameters for exposure to hexachlorocyclopentadiene, allylchloride, epichlorohydrin and endrin. _In_: Chemical Porphyria in Man, J.J.T.W.A. Strik and J.H. Koeman, Ed. Elsevier/North Holland Biomedical Press, New York. p. 55-61.

NCI (National Cancer Institute). 1979. Bioassay of endrin for possible carcinogenicity. Carcinogenesis Tech. Rep. Ser. 12, NCR-CG-TR-12. DHEW Publ. No. (NIH) 79-812.

Nelson, S.C., T.L. Bahler, W.V. Hartwell, D.A. Greenwood and L.E. Harris. 1956. Serum alkaline phosphatase levels, weight changes, and mortality rates of rats fed endrin. J. Agric. Food. Chem. 4: 696-700.

NIOSH (National Institute for Occupational Safety and Health). 1978. Pocket Guide to Chemical Hazards. 191 p.

NRC (National Research Council). 1977. Drinking Water and Health. National Research Council Safe Drinking Water Committee. National Academy Press, Washington, DC. Vol. 1.

Ohlendorf, H.M., D.M. Swineford and L.N. Locke. 1981. Organochlorine residues and mortality of herons. Pestic. Monit. J. 14: 125-135.

Ottevanger, C.F. and N.J. Van Sittert. 1979. Relation between anti-12-hydroxyendrin excretion and enzyme induction in workers involved in the manufacture of endrin. In: Chemical Porphyria in Man, J.J.T.W.A. Strik and J.H. Koeman, Ed. Elsevier/North Holland Biomedical Press, New York. p. 123-129.

Ottolenghi, A.D., J.K. Haseman and F. Suggs. 1974. Teratogenic effects of aldrin, dieldrin, and endrin in hamsters and mice. Teratology. 9: 11-16.

Pandey, B.B. 1978. A note on endrin poisoning in bullocks. Indian Vet. J. 55: 253.

Park, B.H. and T.P. Lee. 1980. Effects of pesticides on human leukocyte function. HHS Publ. (FDA). FDA-80-1074. p. 273-274.

Pawar, S.S. and M.S. Kachole. 1978. Hepatic and renal microsomal electron transport reactions in endrin treated female guinea pigs. Bull. Environ. Contam. Toxicol. 20: 199-205.

Phillips, D.D., G.E. Pollard and S.B. Soloway. 1962. Thermal isomerization of endrin and its behavior in gas chromatography. J. Agric. Food Chem. 10: 217-221.

Probst, G.S., K.E. McMahon, L.E. Hill, et al. 1981. Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 compounds. Environ. Mutagen. 3: 11-32.

Radeleff, R.D. 1956. Hazards to livestock of insecticides used in mosquito control. Mosquito News. 16: 79-80.

Rapaport, E., E. Farjoun, S. Shlosberg and M.N. Egyed. 1979. Endrin poisoning in a herd of goats. Refu. Vet. 36: 142-143.

Reddy, O.B., V.D. Edward, G.J.S. Abraham and R.K. Venkaliswara. 1966. No title provided. (Cited in: Jager, 1970d)

Rees, G.A.V. and L. Au. 1979. Use of XAD-2 macroreticular resin for the recovery of ambient trace levels of pesticides and industrial organic pollutants from water. Bull. Environ. Contam. Toxicol. 22: 561-566.

Reichel, W.L., E. Cromartie, T.G. Lamont, B.M. Mulhern and R.M. Prouty. 1969. Pesticide residues in eagles. Pestic. Monit. J. 3: 142-144.

Reins, D.A., J.A. Rieger, Jr., W.B. Stavinoha and L.B. Hinshaw. 1966. Effect of endrin on venous return and catecholamine release in the dog. Can. J. Physiol. Pharmacol. 44: 59-67.

Reuber, M.D. 1978. Carcinomas, sarcomas and other lesions in Osborne-Mendel rats ingesting endrin. Exp. Cell. Biol. 46: 129-145.

Reuber, M.D. 1979. Carcinogenicity of endrin. Sci. Total Environ. 12: 101-135.

Revzin, A.M. 1966. The effects of endrin on telencephalic function in the pigeon. Toxicol. Appl. Pharmacol. 9: 75-83.

Revzin, A.M. 1968. Effects of chronic endrin administration on brain electrical activity in the squirrel monkey. Fed. Proc. 27: 597.

Richardson, L.A., J.R. Lane, W.S. Gardner, J.T. Peeler and J.E. Campbell. 1967. Relationship of dietary intake to concentration of dieldrin and endrin in dogs. Bull. Environ. Contam. Toxicol. 2: 207-219.

Robinson, J. 1962. Shell Research Ltd. Private communication to K.W. Jager. (Cited in: Jager, 1970d)

Safe, S. and O. Hutzinger. 1973a. Mass Spectrometry of Pesticides and Pollutants. CRC Press, Cleveland, OH. p. 124.

Safe, S. and O. Hutzinger. 1973b. Mass Spectrometry of Pesticides and Pollutants. CRC Press, Cleveland, OH. p. 23.

SANSS Data Base. 1983. Endrin nomenclature, indexing terms and synonyms, June.

Sharma, R.D. and O.P. Gautam. 1971. Experimental endrin poisoning in calves. J. Res. (Punjab Agric. Univ.) 8: 394-403.

Sherman, M. and M.M. Rosenberg. 1954. Subchronic toxicity of four chlorinated dimethanonaphthalene insecticides to chicks. J. Econ. Entomol. 47: 1082-1083.

Sittig, M. 1977. Pesticide Process Encyclopedia. Noyes Data Corp., Park Ridge, NJ. p. 226-229.

Spaulding, J.E. 1972. Pesticide and heavy metal residues. Proc. Meat Industry Res. Conf., Am. Meat Inst. Foundation, Chicago, IL.

Speck, L.B. and C.A. Maaske. 1958. The effects of chronic and acute exposure of rats to endrin. Am. Med. Assoc. Arch. Ind. Health. 18: 268-272.

Stickel, W.H., T.E. Kaiser and W.L. Reichel. 1979a. Endrin versus 12-keto-endrin in birds and rodents. Am. Soc. Test. Mater. Tech. Publ. 693: 61-68.

Stickel, W.H., W.L. Reichel and D.L. Hughes. 1979b. Endrin in birds: Lethal residues and secondary poisoning. Dev. Toxicol. Environ. Sci. 4: 397-406.

Taylor, D.G. 1980. NIOSH Manual of Analytical Methods, U.S. DHHS, Vol. 6, Method S-284. p. 80-125.

Telang, S., C. Tong and G.M. Williams. 1981. Induction of mutagenesis by carcinogenic polycyclic aromatic hydrocarbons but not by organochlorine pesticides in the ARL/HGPRT mutagenesis assay. 12th Ann. Meet. Environ. Mutagen Soc. Environ. Mutagen. 3: 359.

Terriere, L.C., U. Kiigemagi and D.C. England. 1958. Endrin content of body tissues of steers, lambs, and hogs receiving endrin in their daily diet. J. Agric. Food Chem. 6: 516-518.

Terriere, L.C., G.H. Arscott and U. Kiigemagi. 1959. The endrin content of eggs and body tissue of poultry receiving endrin in their daily diet. J. Agric. Food Chem. 7: 502-504.

Tessari, J.D., L. Griffin and M.J. Aaronson. 1980. Comparison of two cleanup procedures (Mills, Onley, Gaither versus automated gel permeation) for residues of organochlorine pesticides and polychlorinated biphenyls in human adipose tissue. Bull. Environ. Contam. Toxicol. 25: 59-64.

Tewari, S.N. and I.C. Sharma. 1978. Study of the distribution of chlorinated organic pesticides in different autopsy materials of human poisoning cases using TLC and UV spectrophotometric techniques. Chem. Era. 14: 215-218.

Treon, J.F. and F.P. Cleveland. 1955. Toxicity of certain chlorinated hydrocarbon insecticides for laboratory animals, with special reference to aldrin and dieldrin. J. Agric. Food Chem. 3: 402-408.

Treon, J.F., F.P. Cleveland and J. Cappel. 1955. Toxicity of endrin for laboratory animals. J. Agric. Food Chem. 3: 842-848.

U.S. DHHS (U.S. Department of Health and Human Services). 1978. Occupational health guideline for endrin. In: Occupational Health Guidelines for Chemical Hazards, F.W. Mackison, R.S. Stricoff and L.J. Partridge, Jr. Ed. DHHS (NIOSH) Publ. No. 81-123.

U.S. DHHS (U.S. Department of Health and Human Services). 1982. National Toxicology Program Annual Plan Fiscal Year 1982. NTP-81-94. p. 53.

U.S. EPA. 1971. Pesticide residues in ambient air. Div. Pestic. Comm. Studies, Chamblee, GA.

U.S. EPA. 1975. National interim primary drinking water regulations. December 24. Federal Register. 40(248): 59566-59588.

U.S. EPA. 1979. Reviews of the environmental effects of pollutants: XIII Endrin. HERL, ORD, Cincinnati, OH. EPA 600/1-79-005.

U.S. EPA. 1980a. Ambient Water Quality Criteria for Endrin. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-047.

U.S. EPA. 1980b. Carbon adsorption isotherms for toxic organics. EPA 600/8-80-023. p. 194-195.

Vrij-Standhardt, W.G., J.J.T.W.A. Strik, C.F. Ottevanger and N.J. Van Sittert. 1979. Urinary D-glucaric acid and urinary total porphyrin excretion in workers exposed to endrin. In: Chemical Porphyria in Man, J.J.T.W.A. Strik and J.H. Koeman, Ed. Elsevier/North Holland Biomedical Press, New York, p. 113-121.

Walsh, G.M. and G.B. Fink. 1972. Comparative toxicity and distribution of endrin and dieldrin after intravenous administration in mice. Toxicol. Appl. Pharmacol. 23: 408-416.

Wang, H.H. and S. Grufferman. 1981. Aplastic anemia and occupational pesticide exposure: A case-control study. J. Occup. Med. 23: 364-366.

Weeks, D.E. 1967. Endrin food-poisoning. A report on four outbreaks caused by two separate shipments of endrin-contaminated flour. Bull. WHO. 37: 499-512.

White, D.H. 1979. Nationwide residues of organochlorine compounds in wings of adult mallards and black ducks, 1976-77. Pestic. Monit. J. 13: 12-16.

Williams, D.T., F.M. Benoit, E.E. McNeil and R. Otson. 1978. Organochlorine pesticide levels in Ottawa drinking water, 1976. Pestic. Monit. J. 12: 163.

Williams, G.M. 1980. Classification of genotoxic and epigenetic hepatocarcinogens using liver culture assays. Ann. N.Y. Acad. Sci. 349: 273-282.

Witherup, S., K.L. Stemmer, P. Taylor and P. Bietsch. 1970. The incidence of neoplasms in two strains of mice sustained on diets containing endrin. Kettering Lab., Univ. Cincinnati, Cincinnati, OH.

Wolfe, H.R., W.F. Durham and J.F. Armstrong. 1963. Health hazards of the pesticides endrin and dieldrin. Arch. Environ. Health. 6: 458-464.

Wolfe, H.R., W.F. Durham and J.F. Armstrong. 1967. Exposure of workers to pesticides. Arch. Environ. Health. 14: 622-633.

Zabik, M.J., R.D. Schuetz, W.L. Burton and B.E. Pape. 1971. Photochemistry of bioactive compounds: Studies of a major photolytic product of endrin. J. Agric. Food Chem. 19: 308-313.